EDITORIAL

Abuse-deterrent formulations approval reform: Will clinical correctness or real-world results be used to address the nation's opioid crisis: "Noninterference" as a new approval standard

Dan Cohen, MA/LS

ABSTRACT

To further the public policy objectives of Congress and the country, legislators should now insist that abuse-deterrent formulations (ADFs) be deployed for every C-II opioid and stimulant. The need for these innovative technologies has never been greater. And to most efficiently incentivize innovators to develop and deploy the most effective and modern deterrents, a new and simpler regulatory approval standard for ADF should be adopted by the U.S. Food and Drug Administration. That standard, based on a concept of "Noninterference" increases the potential for a much earlier deployment of ADFs in a broad range of products and allows deterrence to play its most effective role in combatting the national opioid crisis.

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INTRODUCTION

Opioid abuse in the United States is a serious public health emergency. Appropriately addressing this crisis requires a broad set of strategies that unquestionably includes federal and state elected officials, public health administrators, families, and the pharmaceutical industry.

An estimated 93 Americans die each day due to opioid misuse and abuse. As recently as 2015, more than 15,000 people in the United States died from prescription opioid overdoses, according to the Centers for Disease Control and Prevention. Including illicit opioid use, the number of deaths increased to 33,000 in that same year.

The federal government has put intense focus on the need to devise a public strategy to combat opioid abuse, while also preventing overdose and death. Federal officials are moving quickly to combat the rampant crisis in communities throughout the nation, ranging from rural towns in Kentucky to metropolitan areas such as Boston. To accomplish these critical goals, government policy needs to take the "next step" and move beyond treatment approaches to addiction and adopt prevention strategies that deter prescription drug abuse at its earliest stages.

Abuse-deterrent formulations (ADFs) are one key component in this broad effort to reduce prescription drug abuse and to implement an appropriate focus of public policy. Yet regulatory approval standards for new ADF products confound policymakers and innovators, causing a misunderstanding of both the expected benefits of deterrence and approval standards that work in the lab but do not reflect the "real-world" of prescription drug abuse.

Abuse deterrence is the most "shovel ready" approach to this public health crisis and a critical aspect of the prevention paradigm—if government is ready to embrace it. Last July, Congress passed the Comprehensive Addiction and Recovery Act, or CARA, the first major federal addiction legislation in several years and the most comprehensive effort undertaken to date to address the opioid epidemic. In December 2016, Congress also passed the 21st Century Cures Act that expedited the discovery, development, and delivery of new treatments and cures in biomedical research. To borrow an old adage, an ounce of prevention (ADF) can be worth a pound of twenty-first century "Cures."

To further the public policy objectives of Congress and the country, legislators should now

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insist that ADF be deployed for every C-II opioid and stimulant. The need for these innovative technologies has never been greater. And to most efficiently incentivize innovators to develop and deploy the most effective and modern deterrents, a new and simpler regulatory approval standard for ADF should be adopted by the U.S. Food and Drug Administration. That standard, based on a concept proposed below, of "Noninterference," increases the potential for a much earlier deployment of ADF in a broad range of products and allows deterrence to play its most effective role in combatting the national opioid crisis.

WHAT IS ADF?

The most relevant prevention program is deterrence that occurs prior to abuse or helps prevent the potential abuser from progressing from oral to higher-risk non-oral prescription drug abuse. It is in this latter area that ADFs have the most relevance. Currently, there is no abuse-deterrent that combats the most ordinary form of abuse—oral abuse (some ER/LA products do have some limited oral abuse-deterrent properties by making the pill more difficult to chew). In other words, there is no "smart pill" that can distinguish between a patient swallowing a prescribed analgesic treatment and an abuser that is seeking the same product to get high.

But multiple ADF technologies do exist that deter the far more perilous forms of abuse—primarily intravenous and intranasal abuse. "Analysis of acute health events recorded by poison centers indicates that death or major effects are twice as likely to occur with intentional abuse of prescription opioids via non-oral routes of administration than ingestion alone. Effective interventions to prevent abuse via non-oral routes of solid dosage forms of prescription opioids, such as ADFs could have a significant public health impact."*

ADF focuses primarily on these critical areas. Public policy support by elected and regulatory officials must concentrate on technologies that exist today to save lives and build a path for future technological breakthroughs. Waiting for the "hoped for" technological advances of tomorrow prolongs the crisis and will cost lives.

Fundamental obstacles exist, however, in how industry and the U.S. Food & Drug Administration (FDA) determines which products receive what type of ADF label. Even more basic, there is not yet an agreement between regulators and the industry on what it means to be abuse-deterrent and how to measure success. The need to bridge this gap is critical to fighting prescription drug abuse. Time is of the essence. While discussion over regulatory end points and outcomes continues, abuse charges forward without real-world prevention.

All parties need to acknowledge the multiple studies that suggest opioid abusers typically abuse several different drugs before they progress to opioids. It should also be acknowledged that abusers are generally aware of the risks associated with opioid abuse. Therefore, prevention must begin as early in the abuse cycle as technically feasible. Policymakers need to take reasonable risks to deploy prevention strategies that hold the promise of incremental improvements over current policy—especially if patient treatment can be protected.

Additionally, policymakers should access and read postings on the drug abuse Web site, BlueLight.org,† recommending tampering methods for prescription drug abuse. The plain reading suggests that there is a conscious decision to try opioids by the abuser. Thus, the core question for most abusers becomes—what opioid shall I abuse? The answer is generally that they abuse what their friends are abusing, which in turn relies on which drug (licit or illicit) happens to be most available. Adopting policies or legislation that restrict access to certain products appears functionally naive in the face of the well-organized abuse community.

As policies are developed to combat prescription drug abuse, it is important to note that "[p]rescription opioid abuse via non-oral routes is associated with higher risk. . . (t)his is clearly linked to a dose-effect in that non-oral routes require alteration of the product resulting in rapid release of the active ingredient. While many interventions have been launched in recent years to combat the prescription drug abuse epidemic, altering these drugs for abuse purposes continues and additional interventions are warranted."‡

*Medical outcomes associated with prescription opioid abuse via oral and non-oral routes of administration, *Drug and Alcohol Dependence*, 28 March 2017, Green, J. et. al. 140.

†*www.bluelight.org/vb/forum.*

‡Medical outcomes associated with prescription opioid abuse via oral and non-oral routes of administration, *Drug and Alcohol Dependence*, 28 March 2017, Green, J. et. al. 144.

In the early days (before the 1980s), the opioid of choice was usually heroin. Since that time, the "abuse market" transitioned to prescription opioids in the 1990s and 2000s as they became more readily available, had the advantage of being predictable, and were often cheaper because the healthcare system provided them for a co-pay (or because of a greater prevalence, they were even more available to be stolen from the family medicine cabinet).

Recent data suggests that there is a gradual switching back to heroin because it is now a much cheaper alternative to prescription drugs, and supply lines have made it more widely available. Drug abuse is as price sensitive as any industry; raising the "cost" (in time, dollars, and amount of moiety accessible) of abusing prescription drugs by including an ADF technology will be expected to divert abusers to older, more readily abusable drugs. Diversion from Abuse-deterrent Opioids to existing highly abusable opioids is an expected outcome of successful ADF deployment. This result would allow the FDA to exercise its authority to remove the readily abusable opioid from the market in favor of the ADF version of the same moiety.

PUBLIC POLICY

Legislators should review the existing data demonstrating diversion and insist on ADF deployment, through the U.S. FDA, to adopt an incremental improvement standard for the addition of ADF into CII opioids and stimulants. Using as a model the Corporate Average Fuel Economy (CAFE) performance standards, enacted into law in 1975 (Title V, Energy Policy Conservation Act), federal legislation, or regulation, can require the FDA to approve ADF by a date certain—without picking any technology "winner" or investing any taxpayer funds. The CAFE standards have governed the fuel economy of new passenger automobile fleets in the United States for the past 32 years—relying solely on manufacturers to develop and advance the technology needed to meet the standard. Congress can use the CAFE model to adopt a similar requirement for pharmaceutical companies to develop effective ADF.

Safety and efficacy outcomes for the intended patient population for the treatment of pain by opiate analgesics are well established. The purpose of the addition of an ADF is to reduce and/or deter tampering. "[O]f all the interventions, ADFs are currently the only tools that impose a direct barrier to prescription drug abuse specifically through non-oral routes."[§]

This critical function of deterring risky forms of abuse (intravenous or intranasal) is the potential public health benefit sought by ADF development. It is an important part of the ADFs discussion to remember that they are meant to deter or prevent abuse in a **non-intended** population, not the intended patient population. As this portion of product (mis)use is both a small and unknown number, the appropriate response requires a public health policy approach with a national prevention strategy—an approach similar to that of U.S. vaccine policies.

The addition of ADF in opioids, by design, does not interfere with the net analgesic benefit present in non-ADF versions of the same therapeutic product. All FDA ADF approvals to date, as well as all pipeline products in the New Drug Applications (NDA)/Investigational New Drugs (IND) development cycle, protect patient treatment and make inappropriate **tampering** of the prescription product more difficult.

MEASURING A "SUCCESSFUL" ADF

One key uncertainty that is impeding the development and deployment of ADF concerns whether any ADF endpoint measured in a clinic, as required and defined by the FDA, adequately predicts real-world abuse. In part, this is due to there being no established threshold for what is a valid endpoint or a clinically important magnitude of effect. Indeed, none of the approved opioids with abuse-deterrent labeling have demonstrated, to FDA's approval, reduced abuse in the real-world because of this lack of definition.

Over the development time for ADF innovators, the challenge for regulatory approval has become clear. The success of an ADF therapy cannot be measured by the scientifically preferred methods of randomized and blinded subjects in triple crossover cohorts in controlled epidemiological clinical trials. ADF is not designed for, nor should it be studied in, "patient" populations. By definition, prescription drug abusers are criminals, breaking federal and state statutes. Abusers are not readily accessible for Institutional Review Board approved trials. The only time the abusers can be "studied" is typically

[§]Ibid., 144.

under three observational conditions—upon arrest, at treatment for overdose, or when voluntarily seeking addiction/abuse treatment.

These same abusers are not the target of ADF. "Professional" abusers have progressed so far into their practice that, when they are arrested, the most appropriate response in the ER or treatment center is medically assisted treatment. ADF is for the opioid naïve or early-stage recreational abusers. It is designed to stop their progression to riskier forms of abusive behaviors.

These misunderstandings of both what is the measure, and who is being measured, confounds the further development of ADF. The FDA has designed a static product guidance with endpoints that are based on the experience of one extended release/long-acting (ER/LA) product (OxyContin), applying the same standard to the development of all ADF technology including Immediate Release (IR) products. This creates additional barriers to ADF development. A Guidance designed to fit one specific technology necessarily stifles innovation. Extending the application of the ER/LA Guidance (8.8 million scripts in 2015) and its application to the most broadly abused products, IR opioids (240 million scripts in 2015)[‖], risks creating a solution that doesn't even begin to solve the problem.

But why is this regulatory system, that relies on unproven clinical endpoint data bearing little resemblance to the real-world patterns of abuse, a problem? The approval process design stifles innovation and denies a potential public health benefit based on a risk paradigm that is both unwarranted and nonexistent.

NONINTERFERENCE -- AN APPROPRIATE APPROVAL STANDARD

To date, while the FDA has approved nine extended release opioids with abuse-deterrent language, with an additional approval for the first immediate-release opioid product, ADF products are a small fraction of the opioid prescription market. And, of these products, only four—OxyContin, Hysingla, Embeda, and Xtampza ER—are marketed.

An additional nearly 30 different NDAs and/or INDs[¶] are on file with the FDA for prospective ADF development. Yet access barriers by managed care organizations limit broader adoption of the ADF technologies.

The FDA publicly stated that it looks forward to a future in which most, or all, opioid medications are available in formulations that are less susceptible to abuse than the formulations that lack abuse-deterrent properties. ADF innovators are trying to respond by developing, licensing, and/or marketing medications, incorporating novel technologies intended to deter abuse. But more needs to be done.

It is important to reconcile the difference between the clinic and the "Street." As noted above, clinical trials of ADF are challenging due to the nature of the abuser and the consequence of the abuse. Yet the FDA can remain true to its science-based mission and still respond to calls for rapid deployment of ADF technology.

Because the ADF is not a "treatment," the clinical measurement of safety and efficacy should be limited to a "noninterference standard." As ADF technologies are either additive to a therapeutic moiety or are New Molecular Entities (NME), Congress could adopt by legislation (or FDA by regulation) guidance that ADFs only need to demonstrate that the addition (matrixed technology or agonist/antagonist formulation) is safe in combination with the underlying drug and does not interfere with the intended patient population treatment. For NME/Prodrugs that create an entity in which the moiety itself has inherent deterrent characteristics, the FDA role is even cleaner—the product must meet existing safety and efficacy standards for treating the intended patient population.

Noninterference as a new standard is premised on the belief that it is an inappropriate burden and misuse of resources to ask the FDA to regulate this area outside of its professional competence and mandate. Simply put, the FDA should not be asked to regulate, by clinical standards, the actions or the reactions of a nonprescribed, unintended, nonpatient population. The ADF portion of a product label and the basis of FDA approvals under the noninterference standard could be limited to a description of the intended mechanism that is believed to deter an opiate naïve or early-stage recreational abuser from misusing the proposed product.

Under noninterference, the FDA would be relieved of an obligation to guess what impact VAS scale measures of "High" and Take Drug Again have on potential abusers, and keep its vital focus on

[‖]National Inpatient Sample (NIS) data for 2015.

[¶]"*FDA Perspective on Abuse-Deterrent Opioid Development*," Douglas C. Throckmorton, MD, Deputy Director for Regulatory Programs CDER, FDA. CBI Abuse Deterrent Formulations Summit, March 7, 2017 slide 23.

safety and efficacy in product development. Label claims could be limited initially to mechanisms of action, and later, validated observational data of rates of diversion and impact on misuse. Properly implemented, noninterference would not change existing patent claims, nor Hatch-Waxman exclusivity[#] concerns. False claim concerns could be appropriately adjudicated in other venues such as the District Courts or at the Federal Trade Commission.

WHY A NONINTERFERENCE STANDARD FOR ADF?

Nearly 100 million people suffer from pain in any given year for a variety of reasons, according to federal officials. Between 9 percent and 12 percent of those who suffer face persistent or chronic pain. In our push to address the opioid epidemic, it is important that we recognize the need to have a balanced approach that aggressively addresses the misuse of prescription drugs while also ensuring that we provide access to pain management for patients in need.

It is encouraging that the federal government is committed to supporting industry efforts to develop technological advancements in the science of medicine that will promote the creation of more ADF. These formulas are critical in the fight to curb opioid abuse, misuse, and diversion. Most importantly, existing technologies and available NMEs can interfere with misusers' efforts to abuse prescription drugs by the intranasal and intravenous routes. Immediate deployment of these existing technologies could positively impact the annual mortality rates if fewer abusers progress to riskier forms of abuse.

The need to accelerate the experiment with ADF technologies has never been greater. The potential societal benefits of allowing ADF claims on CII products that demonstrate deterrent capabilities clearly outweigh risks.

For public policymakers' consideration, what are the reasonably best and worst outcomes/risks to consider? The best-case scenario under non-inference is relatively easy: ADF products work effectively as designed and stem abuse progression at some meaningful level. The worst-case risk scenario under the doctrine of noninterference: therapies including an ADF technology are not more effective at deterring abuse, but do not change the medicinal benefits of the drug. In addition, other short-term considerations include the cost trade-off of moving physician prescribing from primarily generic to "branded" products, a risk balanced by a potential reduction in (expensive) efforts to combat and treat abuse.[**]

This trade-off is an acceptable risk as the approval of ADF opioids would not be expected to change the downward trajectory of physician prescribing. ADF opioids are expected to have a similar risk and similar benefit as current non-ADF opioids when appropriate patient treatment is considered. ADF should be an important inclusion in the effort to mitigate the risk of abuse, misuse, and diversion, but by itself, it cannot solve the problem.

On the "Street" today, millions of drug abusers inhale IR and ER/LA opioids to get a faster high. Some ADF technologies can interfere with that aspect of an abuser's drug liking and deter progression to the riskiest forms of abuse. ". . . (w)hile the majority of intentional abuse cases reported to United States poison centers are via oral route of administration, non-oral routes are frequently reported and **double the risk of death or life-threatening event** (emphasis added). This is a significant finding considering the millions of Americans engaging in nonmedical use of analgesics. ADFs are considered as relevant in reducing injection/inhalation, however do not address oral route of abuse, either intact or otherwise."[††]

The FDA's approval of ADF is part of an effort to take a broad approach to addressing the opioid crisis. Under the Obama Administration, the FDA prioritized ADFs as part of the agency's Opioid Action Plan. The Trump Administration has signaled its intent to continue to focus on the development of this technology as part of their plan to address the opioid crisis.

[#]The Drug Price Competition and Patent Term Restoration Act (known as the "Hatch-Waxman Act") was carefully crafted by Congress with arguably competing goals in mind: to spur new pharmaceutical development and to encourage greater public access to generic drugs. In 1984, Congress enacted the Hatch-Waxman Act as an amendment to the Federal Food, Drug, and Cosmetic Act (the "FFDCA") and the Patent Act. The two main congressional goals Congress sought to address were (1) to encourage innovation in pharmaceutical research and development and (2) to help generic drugs reach the market more quickly.

[**] *"A Cost-Benefit Assessment of Abuse Deterrent Opioids,"* Wayne Winegarden, Ph.D. Sr. Fellow, Business & Economics, Pacific Research Institute, Presentation CWAG Annual Conference July 20, 2015 Slide 4.

[††]Medical outcomes associated with prescription opioid abuse via oral and non-oral routes of administration, *Drug and Alcohol Dependence*, 28 March 2017, Green, J. et. al. 144.

Dr. Scott Gottlieb, President Trump's Commissioner of the FDA, expressed his willingness to work with Congress on expanding the use of ADF technologies during his confirmation hearing before the Senate Health, Education, Labor, and Pensions Committee.

It is important to revolutionize the current approval process for ADF by refocusing the FDA on its strengths. The FDA is well equipped to determine the safety and efficacy of therapeutic treatments; it is less adroit at understanding nonmedical misuse and/or the motivations of a drug abuser. The concept of "noninterference" creates a rational and scientific pathway to ADF approvals as policymakers begin to recognize that "[a]buse-deterrent formulations (are) a small part of the overall prescription opioid market…(but) until they are more widely prescribed we may not realize the potential public health impact."[##] ADFs are an appropriate part of an "all of the above" strategies that are needed to combat prescription drug abuse.

Dan Cohen, Chair, MA/LS, Abuse Deterrent Coalition,[§§] *Washington, DC.*

[##]Ibid, 144.

[§§]The Abuse Deterrent Coalition (ADC), representing nearly 30 Abuse Deterrent Formulations (ADF) innovators, patient advocates, and related organizations, is committed to working with federal officials to address opioid abuse. The Coalition was developed to help tackle opioid abuse through the expanded access of ADF technologies which have been effective in reducing the likelihood of opioid abuse. The ADC understands the need to advance formulations that will support the safe use of opioid medications.