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FDA AND ABUSE DETERRENT OPIOIDS: DON'T FIX THE BLAME. FIX THE PROBLEM

There is no such thing as a medicine that is 100 percent abuse-proof. The only abuse-proof medicine is one that is never prescribed—and for the hundreds of millions of Americans suffering from chronic pain that isn't a viable option. Advancing the regulatory science of abuse deterrence is an important step in the right direction.

Cutting the Gordian Knot of opioid abuse and addiction means more than advancing *the science* of abuse deterrence. It means working with the providers of Continuing Medical Education to develop better curricula. It means validated Risk Evaluation and Mitigation Strategies with more thoughtful purpose, using the tools of the 21st century such as patient and physician apps. It means enhanced and validated reporting tools for post-marketing surveillance. And it means using real world data to provide real world advice. It means using that data for better social science tools that can assist prescribers in determining which patients are likely to abuse—and those for whom abuse is unlikely.

"Abuse deterrence" isn't just a formulation question—it's a systems question.

The Food and Drug Administration (FDA) can play an important role in working to develop and share (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.

The FDA has announced labeling changes and post-market study requirements for opioids, and the agency has signaled interest in using real world outcomes data to amend and update labeling. That's not regulatory mission creep; it's the appropriate application of the agency's Safe Use of Drugs initiative.[1] The way you make a drug "safer" is to ensure that it is prescribed to the right patient and used in the proper manner.

At the last FDA Science Board meeting, more than a few FDA presenters discussed the importance of real world evidence.[2] A logical next step is to utilize that real world evidence to amend product-specific abuse-deterrent labeling to indicate lessons learned outside of the rarified world of the randomized clinical trial environment to assist physicians in using the right product for the right patient.

And real world evidence doesn't just mean recognizing new risks, but also communicating new benefits learned through patient outcomes.

According to the *Journal of Pain*, in a real-world study, abuse by snorting, smoking, and injecting prescription opioids declined by 66 percent after the reformulation of a drug with abuse deterrent properties.[3] And the *New England Journal of Medicine* reported that a new formulation decreased abuse from 35.6 percent of respondents to 12.8 percent in 21 months.[4]

Such changes mark important steps in highlighting the value of individualized patient pain-management programs. Abuse-deterrent technologies are an important step in the right direction. They are part of the solution, but they're not the *whole* solution.

The recent decision by Health Canada not to remove non-Abuse Deterrent Formulation (ADF) opioids from the market puts this issue into the proper perspective:

> ". . . proposed regulations would have required therapeutic products containing controlled release oxycodone to have tamper-resistant properties before they could be sold in Canada. Following the consultation, and a review of the latest scientific evidence, the department has concluded that this specific regulatory approach, requiring tamper-resistance, would not have had the intended health and safety impact. Specifically, requiring tamper-resistant properties on all legitimate preparations of controlled-release oxycodone would have served to eliminate certain lower cost drugs from the market, increasing costs for patients and the health system, while having little to no effect in the fight against problematic opioid use. While the proposed regulations will not move ahead at this time, Health Canada supports efforts to develop strategies that can address problematic opioid use including industry efforts to develop tamper-resistant formulations of drugs."[5]

To better understand the real-world impact of ADF therapies and continue to support innovation in this space, the FDA has required all sponsors of brand name products with approved abuse-deterrent labeling to conduct long-term epidemiological studies to assess their effectiveness in reducing abuse in practice.

And then there's the thorny question of FDA labeling. Product labeling is the basis for articulating the value proposition of a product. And, in the case of categories 3 and 4 opioids, that value is *likely or proven* abuse deterrence. It's harder than it sounds and resides at the eye of the opioids policy hurricane.

Category 3 products, based on pre-approval clinical trials are "expected to reduce abuse." A category 4 product based on real-world evidence "has been shown to reduce abuse"—the Holy Grail of ADF labeling language.

Data definition and generation for categories 3 and 4 are very much still a work-in-progress—as is their relationship to clinical relevance. No absolute magnitude of effect can be set for establishing ADF characteristics. And the FDA continues to talk about the ambiguous totality of evidence standard—which really means using their best regulatory judgment. The FDA recognizes that the ADFs are not failsafe and more data are needed.

One crucial question that deserves more conversation is the nature of the evidence that should be used to decide whether or not a given ADF product "works" to reduce abuse in the "real world." Given the data challenges, it may be almost impossible to ever demonstrate a causal link between a new formulation and an impact on patient abuse —but is that because the product didn't have an effect or our current measurement methodologies and data systems are inadequate to detect it? Are there other ways to conclude that a category 4 level has been achieved? That's the problem that should be keeping the FDA and industry up at night.

The path forward is unclear. Is real world data reliable and robust enough? Should the FDA define and then assign various statistical weights to ADF comparison and population studies? And what about REMS reporting? At the end of the day, the agency can't only look to REMS for risk mitigation but must also seek out data that supports more aggressive abuse deterrent labeling language. Nobody said it was going to be easy.

The challenge is that, when it comes to categories 3 and 4 (and especially 4), there's limited data and (at present) no numerical threshold to define "meaningful reduction" in abuse. Obviously, more work needs to be done in order to refine optimal data sources, study design, statistical methods, and epidemiologic outcomes of interest both developers, regulators, physicians, and patients—and payers.

For ADF innovators, a predictable regulatory pathway towards category 4 labeling will incentivize continued investment and comprehensive reimbursement strategies. For generic manufacturers, defining best practices for "abuse equivalence" programs will allow the Hatch/Waxman paradigm to take effect, driving prices down while also incentivizing further branded innovations. The FDA's recent draft guidance on the development of generic ADF opioids will significantly expedite both the development programs and approval timelines of these products.

Most importantly, a smart public health strategy would be a robust effort to better educate physicians on appropriate prescribing —something the FDA has been calling for regularly. The agency's announcement that it will require short-acting opioid pain medications to carry a boxed warning about the serious risks of misuse, abuse, addiction, overdose and death is an appropriate next step.

Abuse-deterrent technologies are an important step in the right direction. They are part of the solution, but they're not the whole solution. The public health goal is safe, effective, and affordable access to opioid pain relief. Active partnerships between academics, developers, payers, patients, and physicians are crucial. And, as is often the case, the FDA is at the center of the ecosystem.

Abuse deterrence is a worthy goal and will only evolve when all the players work together in a more regular and synchronistic fashion. As the Japanese proverb goes, "Don't fix the blame, fix the problem."

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