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October 30, 2019

Food and Drug Administration
Dockets Management Staff (HFA-305)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
Submitted via regulations.gov

Re: Standards for Future Opioid Analgesic Approvals and Incentives for New Therapeutics to Treat Pain and Addiction; Public Hearing, Docket FDA-2019-N-2514

Dear Food and Drug Administration;

These comments are submitted in response to the Federal Register notice Standards for Future Opioid Analgesic Approvals and Incentives for New Therapeutics to Treat Pain and Addiction, Docket FDA-2019-N-2514. This is a written version of comments made orally at the September 17, 2019, Food and Drug Administration (FDA) public hearing on this topic.

By way of disclosures, I am the Chief Medical Officer with the consulting firm **Pinney Associates**. Through **Pinney Associates**, I advise pharmaceutical companies, primarily those working on CNS-active drugs and new analgesics, on clinical and regulatory strategies for their development programs with an emphasis on assessing the abuse potential of these novel products relative to those currently on the market. I also serve as Chief Medical Officer for Harm Reduction Therapeutics, a nonprofit pharmaceutical company working to bring an affordable naloxone over-the-counter product to the market.

These comments are my own and do not represent those of any company for which **Pinney Associates** provides or has provided consulting services. Additionally, these comments were not vetted with anyone outside of our company, nor did any outside organization compensate me or my colleagues for our time to prepare these comments.

My colleagues and I at **Pinney Associates** agree with the principle that a new opioid analgesic should be able to demonstrate some level of incremental improvement with respect to either abuse potential or to some other relevant safety outcome, such as less respiratory depression, compared to existing Schedule II opioids currently on the market.

However, in today's health care system, even if a novel opioid product were able to demonstrate an incremental benefit over existing products, current policies around product labeling as well as scheduling under the Controlled Substances Act provide little basis for differentiation. As a result, third-party payors have minimal motivation to accept new opioids given that new drugs generally cost more than the legacy and generic products which currently dominate the market.

Comparative Data for New Opioid Analgesics

From the FDA's proposed topics for discussion, I first address whether sponsors of new opioid analgesics should be required to demonstrate some comparative advantage relative to existing analgesics.

For 17 years, I worked at the German pharmaceutical company, Gruenenthal, during which time I was involved in the development of novel analgesics including tapentadol and in the development of abuse deterrent formulations.

It has long been an expectation of the European Medicines Agency (EMA) that sponsors developing novel analgesics include active comparators in their clinical trials.

Given that Gruenenthal was collaborating with Johnson & Johnson on the development of tapentadol, a global clinical development plan was pursued such that the pivotal clinical trials for both the acute pain program as well as the chronic pain program included an appropriate active comparator to meet the requirements of EMA.

Thus, within the respective New Drug Applications (NDAs) submitted to the Agency for tapentadol, the FDA had a substantial amount of data in its hands comparing tapentadol to other opioid agonists with regards to efficacy as well as to safety in both acute and chronic pain indications.

Unfortunately, even though these were data from large randomized well-controlled pivotal trials, accepted by the FDA as the basis for approving the drug, the Agency did not allow any comparator data from these trials in the product label. This was not because the data weren't well-collected and properly tabulated, but simply as a matter of policy.

So, even if a sponsor gets approval for a novel analgesic which has demonstrated clinical benefits over a marketed schedule II opioid, by not allowing any of the relevant data in the label – not to make claims but simply to inform prescribers how the efficacy and safety of the two drugs compare – two things happen. First, companies are left to educate health care providers on these benefits by way of publications, posters and conference talks – all of which are increasingly scrutinized and considered suspect even when the data originate from trials deemed acceptable by the FDA for granting NDA approval. Second, third party payors and other organizations have little reason to encourage uptake of these products due to the undifferentiated label.

Therefore, to incentivize sponsors to develop novel opioids with better safety profiles and to produce comparative data versus currently available opioids in their development programs to support these benefits, allowing these data into the label is one policy change FDA could implement. This could help shift prescribing away from the more commonly prescribed immediate release (IR) Schedule II opioids that are attractive for abuse and account for the majority of prescription opioid overdose deaths.

Post-marketing Challenges

The FDA has specifically asked for ideas regarding pre-marketing incentives for sponsors to encourage them to engage in the development of better opioids.

A commonly utilized incentive by the Agency in the pre-marketing area has come in the form of expedited review mechanisms such as Fast Track, Breakthrough Therapy and

Priority Review. I believe most companies developing abuse deterrent formulations (ADFs) received Fast Track designation, and it may have helped them get their products approved a bit earlier. Yet, the biggest challenge that these companies have faced has been in the post-marketing world.

Market access has proven to be an absolute nightmare for ADFs; they currently constitute a minimal share of the opioid market. This has sent a loud and clear signal to other companies as well as investors to think twice before investing in the development of novel opioid analgesics.

The perverse and frankly deadly policies of third-party payors to favor Schedule II IR opioids over products such as ADFs, has impacted the potential for these products to make a difference with respect to the public health.

This includes the Veterans Administration (VA) whose policy of discouraging the use of these products because they are more expensive is counter to FDA's efforts to transform the market. The VA is likely correct in its claim that the actual rates of abuse of its patient population is low because we know that opioid abuse among properly prescribed pain patients is low. But that conundrum needs to be addressed or the market will not be transformed.

Even buprenorphine, a schedule III partial agonist with a lower risk of respiratory depression, is only allowed by many payors to be prescribed after a patient has failed on two schedule II opioids. The public health impact of this restriction means that many patients are unnecessarily taking a less safe medicine.

Thus, due to these challenges with market access, even with expedited review there remain substantial disincentives for companies to develop safer opioid products.

I spent the last few years at Gruenthal in a "search & evaluation" role. I was involved in the assessment of numerous analgesics, many of which were novel opioids. At **Pinney Associates**, I advise both small biotechnology companies and larger pharmaceutical companies working in this space. There is a lot of very promising science out there. Our understanding of the opioid system and how to better target the receptors has grown immensely in recent years. But companies working in this space are struggling to find investors and development partners due to concerns regarding market access. They have all seen the low market uptake of ADFs and other differentiated opioids like tapentadol and buprenorphine.

To summarize, what can the FDA do?

1) Allow comparative data into product labels. The FDA cannot solve the opioid epidemic by itself, but it can play an important role in regard to the abuse of prescription products by making sure that safer and better products get to market with the relevant comparative data in the label so that prescribers and payors can recognize and understand the benefits.

2) Work with the Department of Health and Human Services, the Veterans' Administration and third-party payors to encourage the prescribing of products for which clinical studies and increasing real world evidence suggest they may carry lower risks of abuse and/or overdose.

3) Engage other relevant federal agencies to produce white papers that elucidate the issues around development and uptake of demonstrably safer opioids analgesics, describe what respective federal agencies can and cannot do, and continue to encourage sponsors to develop more efficacious and safer drugs.

I appreciate the Food and Drug Administration's effort to identify the barriers and potential solutions to the development and marketing of safer opioids. Thank you very much for the opportunity to provide these comments. Please contact me at **Pinney** Associates at jashworth@pinneyassociates.com or tel: 301-718-8440 if you have any questions or need further information.

Sincerely,

Judy Ashworth, M.D.
Chief Medical Officer