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December 2, 2011

Janet Woodcock, MD
Director, Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10923 New Hampshire Avenue
Silver Spring, MD 20993

RE: Docket No. FDA-2011-D-0771
Draft Blueprint for Prescriber Education for Long-Acting/Extended-Release Opioid
Class-Wide Risk Evaluation and Mitigation Strategy

Dear Dr. Woodcock,

While understanding that the Risk Evaluation and Mitigation Strategy (REMS) for extended release and long-acting (ER/LA) opioids and the blueprint for education are efforts to improve opioid safety, we believe there are unaddressed safety issues in the blueprint. We respectfully submit the following concerns.

Physicians dramatically increased their prescribing of opioids for chronic non-cancer pain (CNCP) over the past two decades. Unfortunately, this change in practice was driven by physician education that minimized risks of long-term opioid therapy for CNCP patients and exaggerated benefits. Physicians were given the impression that long-term opioid therapy had been proven safe and effective for CNCP. However, the long-term effectiveness and safety of managing CNCP with opioids has not been established. Surveys of CNCP patients being managed with opioid therapy have shown that many continue to experience significant chronic pain and dysfunction.^{1,2} There is a consensus among experts that available clinical trials are insufficient to establish long-term benefits from this treatment.³ The lack of evidence regarding long-term benefits, coupled with alarming evidence that increased prescribing of opioids is fueling an epidemic of addiction and overdose deaths, means that an educational effort to counter past misinformation and over-prescribing is urgently needed.

Over the past decade, efforts to address increases in prescription opioid abuse and death have attempted to balance risk management strategies to control abuse with the objective, often voiced by industry-funded advocacy groups, to preserve opioids for millions of people with chronic non-cancer pain (CNCP). Despite these efforts, rates of overdose deaths are now four times higher than they were in 1999 and rates of individuals seeking treatment for opioid addiction are six times higher.⁴ Clearly, this approach has failed.

In July 2010, the FDA convened a panel of experts whose majority vote was against the FDA's proposed ER/LA opioid REMS on the grounds that: 1) the focus on ER/LA opioids would not be sufficient since all opioids, not just ER/LA opioids, are being over-prescribed; 2) the pharmaceutical industry is not the best choice for developing scientifically unbiased education about drug use since the industry needs to promote its products, and 3) because the proposed

REMS education programs are not mandatory, many prescribers will continue to prescribe without necessary education that reflects current evidence regarding opioid benefits and risks. These concerns remain unaddressed by the current REMS.

The preponderance of expert opinion, reflected in a recent series of editorials in leading medical journals (see attachments to this letter) is that a substantially more cautious stance toward opioid prescribing for CNCP is now needed.⁵⁻¹² The proposed REMS needs to adequately reflect the results of recent research, clinical experience and changing views reflected in these editorials.

The blueprint implies that when prescribed carefully, benefits of opioid therapy outweigh risks. However, recent studies (not referenced in the blueprint), suggest that long-term opioid therapy for CNCP is not providing good pain relief or improving function for many patients, and is producing serious adverse outcomes in addition to abuse and death, particularly when doses escalate to high levels.¹³⁻¹⁷ The argument that chronic non-cancer pain patients will suffer needlessly if opioid prescribing is reduced, particularly higher dose prescribing common in patients managed with ER/LA opioids, is not grounded in scientific evidence.

Specific comments regarding the blueprint are the following:

Early in the preamble, it is stated “Opioid misuse and abuse, resulting in injury and death, has emerged as a public health problem”. This is misleading, since much injury and death may arise in people using opioids exactly as prescribed, not just those misusing or abusing.

In the second paragraph, data are provided that highlight the problem of non-medical use, but none are provided that highlight the problem of legitimate use that produces adverse outcomes.

The blueprint fails to clearly differentiate prescribing of opioids for acute pain, for palliative care of end-stage and terminal illnesses, and for long-term management of chronic, non-cancer pain. Prescribers must learn how to distinguish risks and benefits for each of these indications. Accumulating evidence and clinical experience now suggests that a more cautious stance toward prescribing opioids for CNCP is required, so this distinction is critically important.

Throughout the document, the ER/LA qualifier should be removed so that the lessons of the educational intervention can be understood to apply to all opioids, and not just to ER/LA opioids. A separate section could emphasize what is different about the ER/LA opioids. For example:

1. Higher doses are utilized, which are therefore more likely to be abused, to cause death, and to cause serious dose-related adverse effects.
2. With a few exceptions, ER/LA opioids are not suitable as a first line opioid (contrary to IIIb, which should be modified).
3. There is no evidence to support previous teaching that ER/LA can provide better analgesia or less abuse risk than immediate release products (needs emphasis in order to correct the record).
4. Commencing ER/LA opioids is often the starting point for high dose opioid therapy, a practice that growing evidence suggests is harmful to patients and increases black market availability of opioids via diversion.

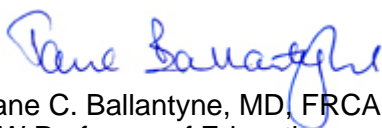
Safety issues are under-represented in the blueprint:

1. Titration should be based on safety, not just on efficacy and tolerability (IIIb)

2. Deaths often occur at night; ER/LA use runs counter to the goals of night-time safety and improved sleep; dangers of concomitant medication use, especially night sedatives, are under emphasized; dangers of obesity and sleep apnea are under emphasized
3. Prolonged QTc interval (and sudden death) is a potential problem for all opioids, not just methadone and buprenorphine, particularly at high dose (VIc)
4. Risks of over-sedation, impaired cognition, falls and fractures and serious bowel obstruction are significant concerns for opioids administered around the clock; ER/LA opioids are labeled for around the clock administration
5. Evidence now exists that people using opioids long-term for CNCP are unlikely to discontinue opioid use, even if analgesia and function are poor, and safety issues arise.¹⁸ This suggests an important role for dependence and addiction during long-term opioid use; a commitment to opioid treatment is often a commitment for life, and should be considered as such when reviewing safety.

In summary, we believe a prescriber education effort to address opioid analgesic overuse will be ineffective unless past misinformation on risks and benefits are explicitly and forcefully corrected. Prescribers are in need of education that will allow them to properly weigh risks versus benefits before initiating long-term treatment with opioids. An educational effort that fails to do this and instead continues to equate compassionate care for CNCP patients with a prescription for opioids is likely to worsen rather than improve the public health crisis that opioid analgesics have precipitated through their widespread, long-term use for CNCP.

Sincerely,



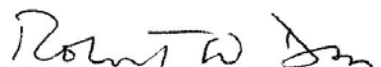
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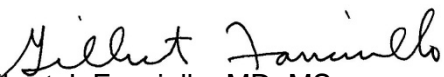
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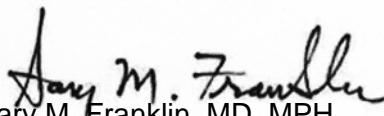



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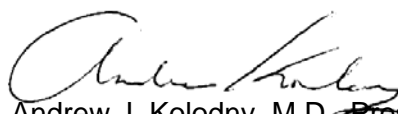
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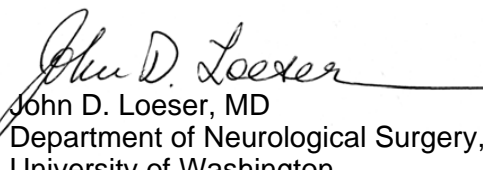

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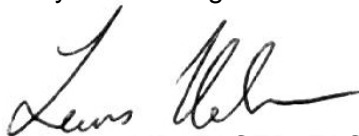

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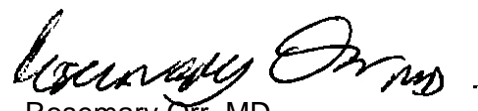

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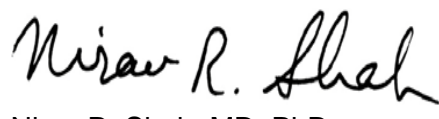

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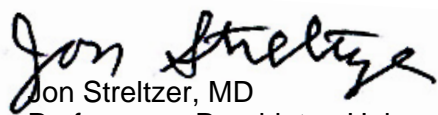

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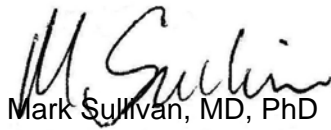

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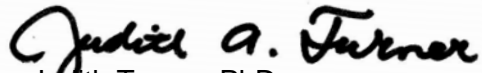

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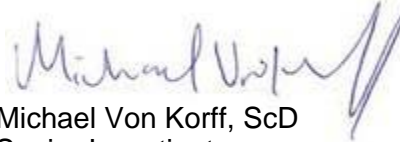
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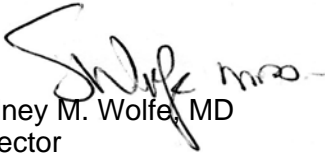
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Enclosures

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