DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Fred Upton
Chairman
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

AUG 12 2015

Dear Mr. Chairman:

Thank you for your letter of July 7, 2015, cosigned by three of your colleagues, concerning ongoing efforts by the Food and Drug Administration (FDA or the Agency) to combat the opioid abuse epidemic and to more effectively incentivize the development and broadened use of evidence-based practices and treatments.

We have restated your questions below in bold, followed by our responses.

1. **Please identify the NIH source and provide the studies referenced that support the FDA's statement in the "Guide to Safe Use of Pain Medicine." Since the statement was made in 2009, does FDA have any updates or further clarifications on the statement?**

The statement cited was in a consumer update from 2009, which is now archived on the *FDA.gov* website. It is not possible to identify the source of the statement at this time. However, there are a number of newer consumer updates and drug safety updates on the website that reflect FDA's current thinking regarding the safety and efficacy of opioid analgesics. These may be found at the following links:

July 2010: Combatting Misuse and Abuse of Prescription Drugs:
http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm220112.htm

April 2011: FDA Acts to Reduce Harm from Opioid Drugs:
http://www.fda.gov/forconsumers/consumerupdates/ucm251830.htm

Sept 2013: Goal of Label Changes: Better Prescribing, Safer Use of Opioids
http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm367660.htm

New Safety Measures Announced for Extended-Release and Long-Acting Opioids from 2014
http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm363722.htm

2. Has FDA reviewed the AHRQ study? If so, how are the studies reflected in FDA policy?

FDA has reviewed AHRQ's report, "The Effectiveness and Risks of Long-term Opioid Treatment of Chronic Pain." The authors conducted a systematic review of electronic databases and clinical trials registries for studies of patients with chronic pain considered for or prescribed long-term opioid analgesics. The key research question that pertained to the effectiveness of labeling and risk management strategies is the following:

In patients with chronic pain prescribed long-term opioid therapy, what is the effectiveness of risk mitigation strategies, including (1) opioid management plans, (2) patient education, (3) urine drug screening, (4) use of prescription drug monitoring program data, (5) use of monitoring instruments, (6) more frequent monitoring intervals, (7) pill counts, and (8) use of abuse-deterrent formulations on outcomes related to overdose, addiction, abuse, or misuse?

In conducting this evaluation, the authors found no studies in which to evaluate the key question and, therefore, concluded that they "found no evidence that risk mitigation strategies were effective."

The labeling changes approved on April 16, 2014, for the extended-release and long-acting (ER/LA) Opioid Analgesics were intended to describe more clearly the risks and safety concerns associated with ER/LA opioids and to encourage appropriate prescribing, monitoring, and patient counseling by prescribers of these drugs.

The central component of the approved Risk Evaluation and Mitigation Strategy (REMS), for the ER/LA Opioid Analgesics is an education program for prescribers (e.g., physicians, nurse practitioners, physician assistants) of these products. The prescriber education is intended to reduce the potential for serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA Opioid Analgesics, while ensuring that patients with legitimate need for these drugs continue to have access to them. The annual assessments for the ER/LA Opioid Analgesic REMS aims to determine whether this strategy is effective in reducing events of interest in patients receiving ER/LA Opioid Analgesics. Under the REMS, manufacturers of the ER/LA Opioid Analgesic are required to make training available to all prescribers of ER/LA opioid analgesics. The sponsors are meeting this obligation by providing educational grants to accredited Continuing Education (CE) providers who are offering training to prescribers at no, or nominal, cost. These CE training programs are required to cover the content and messages of a blueprint developed by FDA for this purpose.

In September 2013, FDA directed the manufacturers of ER/LA Opioid Analgesics to conduct a series of post-marketing studies designed to assess the safety related to long-term use of these products for analgesia. FDA has worked in conjunction with industry to design these studies, which required creative and flexible approaches to address these important issues, as well as innovations in methodology. While these studies are designed to address key issues of importance, including many of those described in the AHRQ report, FDA anticipates that they will spur additional questions and research in this area. These studies are currently underway.

As FDA continues to evaluate these assessments and studies, we will consider, to the extent we deem it appropriate and useful to do so, the views and findings of other stakeholders and experts, including those contained in the AHRQ report.

3. **Does the use of enriched enrollment exclude patients from clinical trials who might have a pre-existing low tolerance for any forms of opioids? What is FDA's justification for permitting enriched enrollment for clinical trials using opioids? Is there a concern that this practice underestimates the risk of abuse?**

Clinical trials using an enriched enrollment design are used to evaluate efficacy and safety for a variety of drug products from a range of therapeutic classes. This type of design can be useful in the evaluation of opioid drug products for several reasons.

- Opioid analgesics have a number of predictable adverse side effects that are related to dose. The side effects can include nausea, vomiting, headache, constipation, and itching for many patients. Patients who are sensitive to these side effects can lessen their effect by starting at lower doses and advancing the dose slowly to optimum pain management. In a clinical setting, with the knowledge that these side effects can be lessened or can diminish over time, prescribers will titrate patients' doses up or down as needed to give them time to adjust. Clinical trial designs, due to blinding and dropout concerns, generally lack sufficient flexibility to permit for a slow titration over time for sensitive patients. As a result, patients in a clinical trial who are sensitive often drop out due to these side effects, which affect the ability to perform proper statistical evaluation. Enriching the study for patients who can tolerate, or do not experience, these side effects allows patients to remain in the study long enough to assess efficacy over the study period.
- Clinicians experience patients who may have idiosyncratic responses to opioid agents such that patients may respond to one opioid but not to another. Enriched designs allow assessment of whether patients feel they respond to the study opioid. If patients seem to have a good efficacy response, they are then randomized in an appropriate blinded fashion to either stay on the drug or be switched (withdrawn) to placebo. This approach allows for an assessment of efficacy for patients while on blinded therapy, and also has the advantage of using a much smaller number of patients.
- Because the group of patients who remain in an enriched study may not reflect the general population, the clinical trial section of the product labeling describes how many of the original group of subjects did not tolerate or respond positively to the study opioid. In this way, prescribers receive information on the population enrolled and the percentage of people started on the study opioid who did not meet the enrichment criteria.

When clinical trials are conducted to evaluate efficacy or safety, whether they are of an enrichment or standard design, they are not able to evaluate the risk of abuse. Patients enrolled in clinical trials of opioids are informed ahead of time that there will be substantial oversight, including screening for illicit drug use and close monitoring and accounting of the use of study medication. In addition, patients who may be at high risk for abuse due to, for instance, a history of substance abuse or severe mental illness, are generally excluded from clinical trials, as they may not be compliant with the study protocol. This sets up an environment where any detected

abuse will not adequately predict abuse in a clinical setting. That is why abuse assessments are required as post-marketing requirements. This is exemplified for the ER/LA opioids, where abuse assessment is not part of the clinical trials but is addressed using a number of epidemiological and observational studies crafted to evaluate the risk of abuse, among other endpoints, using a variety of methods.

4. Please identify and provide the studies that FDA relied on in its decision to exempt manufacturers of immediate-release opioids from the black box warning required for extended release opioids.

FDA requires certain boxed warnings for ER/LA opioids based on FDA's assessment of the risks associated with that class of products. FDA previously concluded that there were disproportionate safety concerns associated with these products, compared to immediate-release (IR) opioids. This led FDA to approve a REMS for the ER/LA opioids in July 2012 and, in September 2013, announce class-wide safety labeling changes and new post-market study requirements for these products.

In February 2014 Purdue Pharma submitted a petition (FDA-2014-P-0205) to FDA disputing FDA's previous assessments of the relative safety concerns associated with ER/LA and IR opioids. Purdue's petition states that IR opioids are associated with the same potential adverse consequences as ER/LA opioid analgesics generally, including the risks of abuse, misuse, and overdose, with comparable incidences and public health ramification, and requests, among other things, that the safety labeling information for IR and ER/LA opioids convey the same warnings and precautions regarding the risks of opioid use and misuse. That petition is under active consideration by the Agency.

5. What is FDA's policy on when an advisory panel is used to review Schedule II drugs?

FDA organized a number of advisory committee meetings to discuss issues associated with Schedule II opioid analgesics. These have included advisory committees to discuss the following products:

- May 5, 2008 — OxyContin (extended-release oxycodone hydrochloride)
- May 6, 2008 — Fentora (immediate-release fentanyl)
- November 13, 2008 — Remoxy (extended-release oxycodone hydrochloride)
- November 14, 2008 — Embeda (extended-release morphine sulfate and naltrexone)
- September 23, 2009 — Exalgo (extended-release hydromorphone hydrochloride)
- September 24, 2009 — OxyContin (extended-release oxycodone hydrochloride)
- April 22, 2010 — Acurox (immediate-release oxycodone hydrochloride)
- July 22-23, 2010 — Extended-Release and Long-Acting Opioid REMS
- October 21, 2010 — Embeda (extended-release morphine sulfate and naltrexone)
- October 22, 2010 — OxyContin (extended-release oxycodone hydrochloride)
- October 29-30, 2012 — Hydrocodone
- December 7, 2012 — Zohydro (extended-release hydrocodone)
- July 17, 2013 — Moxduo (immediate-release morphine sulfate and oxycodone hydrochloride), cancelled

- April 22, 2014 — Moxduo (immediate-release morphine sulfate and oxycodone . hydrochloride)
- July 7, 8 2015 cancelled[1] — OxyContin (extended-release oxycodone hydrochloride),

Under section 505(s) of the Federal Food, Drug, and Cosmetic Act, before approving a drug with an active ingredient that has not been previously approved by FDA in another product, FDA must either refer that drug to an advisory committee or provide in the action letter for the drug a summary of the reasons why FDA did not refer the drug to an advisory committee before approval. Under most other circumstances, FDA has discretion in determining whether to convene an advisory committee. When considering whether to convene an advisory committee, FDA generally considers the following three factors:

(a) Is the matter at issue of such significant public interest that it would be highly beneficial to obtain the advice of an advisory committee as part of the Agency's regulatory decision-making process?

(b) Is the matter at issue so controversial that it would be highly beneficial to obtain the advice of an advisory committee as part of the Agency's regulatory decision-making process?

(c) Is there a special type of expertise that an advisory committee could provide that is needed for the Agency to fully consider a matter?

In the event that one or more of these factors is present, the matter at issue should generally be referred to an advisory committee. Conversely, FDA generally refrains from referring a matter if none of these factors is met. This policy is grounded in the recognition that FDA has limited resources and that referring a matter to an advisory committee requires a substantial expenditure of resources and time. By prioritizing matters according to the factors above, FDA helps ensure that the finite resources of its advisory committee program are devoted to consideration of the most important matters, including those matters in which the Agency would most benefit from the advice of outside experts.

The three factors described above are often met in the following circumstances:

- FDA is evaluating a first-of-a-kind, first-in-class medical product for human use.
- FDA is evaluating a medical product for a significant new indication.
- FDA is evaluating a novel product or use of new technology.
- FDA is evaluating a medical product that involves a significant diagnostic, therapeutic, or preventative advance.

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[1] This meeting was cancelled because, as the manufacturer, Purdue Pharma L.P., acknowledged publicly, the supplemental new drug application was withdrawn. For more information, please see *http://www.fda.gov/AdvisoryCommittees/Calendar/ucm448718.htm.*

- FDA's assessment of the risk/benefit ratio of a product or class of products is likely to be controversial or it appears that the risks and benefits are of similar magnitude, especially where the products may have a narrow therapeutic effect.

- FDA has significant safety concerns about a class of products. This scenario includes such concerns in pre- or post-market situations (e.g., significant safety concerns relating to the pre-market review of a medical product regulated by FDA, or significant safety concerns relating to the post-market review of such a medical product, including significant concerns about adverse event reports or other data that signal a potential safety issue).

- FDA has significant questions or concerns about the use of a product in certain subpopulations (e.g., pediatric dosing or a newly discovered contraindication).

- FDA has significant questions or concerns about a study, including a clinical trial, post-market assessment, or product development protocol (PDP). The questions or concerns may relate to any aspect of such a study, including human subject protection, novel endpoints or surrogates, the study's design, or its results.

- FDA personnel have a significant difference of scientific opinion on a complex matter, for example, on the interpretation of data or judgments about the risk/benefit ratio of a regulated product.

- FDA has questions or concerns involving the intersection of several scientific disciplines.

6. **Why did the FDA remove mandatory training for prescribing physicians for opioid drugs from its initial design of the Risk Evaluation and Mitigation Strategy (REMS) for opioid drugs?**

7. **Why did the FDA remove patient registries for opioid drugs from its initial design of REMS for opioid drugs?**

Response to questions 6 and 7:

As part of the process that culminated in the development of the ER/LA Opioid Analgesic REMS, FDA convened a series of meetings with key stakeholders, industry, and the general public. The meetings were held on February 10, 2009, March 3, 2009, May 4 and 5, 2009, May 27 and 28, 2009, and December 4, 2009. These meetings were followed by an advisory committee meeting held on July 22 and 23, 2010.

Given the large number of patients and prescribers who would be impacted by this new REMS, substantially larger numbers than any previous REMS, and considering that the REMS was to be imposed on the holders of the approved applications of the products covered by the REMS, FDA determined that the most appropriate structure of the REMS was to require the drug product companies to make training available to prescribers of ER/LA opioid analgesics, based on an educational blueprint developed by FDA, and to make a patient counseling document available

for prescribers to provide to patients. In particular, the REMS requires that the prescriber education include information on weighing the risks and benefits of opioid therapy, choosing patients appropriately, managing and monitoring patients, and counseling patients on the safe use of these drugs. The prescriber education is also required to include general and product-specific information concerning ER/LA Opioid Analgesics. It is also required to encourage prescribers to use the patient counseling document as part of the discussion when prescribing opioid analgesics to help inform patients about the safe use of these products, including how to use and store them safely. The REMS also requires that patients receive Medication Guides when they pick up their prescriptions. Medication Guides provide information in patient-friendly language about drugs' risks and how to use them safely.

To make this training mandatory would require that the companies holding the applications of the ER/LA Opioid Analgesic create a system whereby they would track the training of all prescribers of opioids, effectively duplicating the DEA registration system. It would also have been necessary to create a closed pharmacy system whereby prescriptions from prescribers who had not completed the training would be rejected by pharmacies. Creating a new system could be extremely burdensome on prescribers and the entire retail pharmacy structure, given the large number of patients and prescribers who would be impacted by the REMS.

Similarly, to require patient registration would also be duplicative of the prescription drug monitoring programs that have been developed by the states, which provide many more advantages such as the ability of prescribers to access the system to determine whether their patients are obtaining opioid analgesics from other prescribers.

Feedback obtained from prescribers, patients, and pharmacists consistently raised concerns that mandatory prescriber training, patient registries, and the necessary associated pharmacy systems for the ER/LA Opioid Analgesic REMS would be unduly burdensome to all involved, substantially reducing access to patients in need of opioid medication, and would be extremely expensive to design and implement, given the large number of patients and prescribers who would be impacted by the REMS, resulting in significant costs passed on to the health care system.

8. How does the FDA evaluate the effectiveness of REMS for opioid drugs?

The manufacturers for the products subject to the ER/LA Opioid Analgesics REMS (also referred to as the REMS Program Committee (RPC)) are required to conduct evaluations of the REMS and to submit REMS assessment reports to FDA on an annual basis. The information contained in these reports includes the number of trainings taken by ER/LA opioid prescribers, results of patient and prescriber knowledge surveys, long-term evaluation studies of knowledge retention and prescribing behavior changes following the ER/LA Opioid Analgesics REMS education, changes in prescription utilization over time, and surveillance data for events of interest. FDA's review of the assessment reports includes multiple offices within the Center for Drug Evaluation and Research to determine if the REMS is achieving its goals or if modifications are needed.

9. What evidence does FDA have showing that REMS for opioid drugs is effective?

The science of assessing the effectiveness of REMS is still relatively new, and the metrics, data sources, and methodologies to assess REMS continue to evolve.

Due to the voluntary nature of the training for this program, as well as the time required to develop and launch an adequate number of REMS-compliant CE activities, the Agency expected that the impact of the ER/LA Opioid Analgesics REMS would likely not be seen in the initial few years, post implementation. The 2015 REMS assessment was the first that included prescriber knowledge surveys and an assessment of whether certain milestones for prescriber training have been reached. The FDA review of the 2015 ER/LA Opioid Analgesic REMS report is ongoing. We have noted in the 2014 REMS assessment report, however, a statistically significant reduction in the number of prescriptions for ER/LA Opioid Analgesics and IR opioids, as well as decreases in event rates for the majority of outcomes assessed (abuse in both adults and adolescents, misuse, major medical outcomes, hospitalizations/deaths, deaths, ED visits, unintentional therapeutic errors, pediatric unintentional general exposures, and pediatric ED visits) from the pre-REMS implementation period to the active period from the databases provided in the assessment. These reductions and decreases are not solely attributable to the ER/LA Opioid Analgesics REMS, as there are many ongoing efforts in addition to the ER/LA Opioid Analgesics REMS to raise awareness of the risks and curb inappropriate prescribing of opioids.

As with any method or data source used to support program evaluation, there are limitations. Many of the data sources provided in the ER/LA Opioid Analgesics REMS assessments that evaluate adverse events of interest are not designed specifically to address the impact of the REMS on these events. We continue to evaluate data from these sources due to the limited availability of appropriate sources at this time. For this reason, we continue to advise caution in the interpretation of these data and have encouraged the REMS Program Committee to continue to develop the appropriate data and methodologies for misuse and abuse-related analyses.

10. In light of the national opioid abuse epidemic, how does FDA believe that risk mitigation strategies can be improved?

As stated in Dr. Throckmorton's testimony to the Energy and Commerce Subcommittee on Oversight and Investigations on May 1, 2015, FDA continues to support mandatory education as a component of risk management for all opioids.

Thank you, again, for your interest in this important matter. Please let us know if you have any further questions. The same letter has been sent to your cosigners.

Sincerely,

for Thomas A. Kraus
Associate Commissioner
for Legislation