November 27, 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

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 FDA,

On behalf of Advocates for the Reform of Prescription Opioids, Inc. (ARPO), I submit these comments on the FDA’s Draft Blueprint for Prescriber Education for Long-Acting/Extended-Release Opioid Class-Wide Risk Evaluation and Mitigation Strategy (Draft Blueprint). ARPO formed earlier this year with the goal of ending the epidemic of death and addiction caused by prescription opioid drugs by ensuring that opioids are regulated, marketed, prescribed and used in an evidence-based manner. Many of our members are bereaved parents who lost a child to prescription opioids. In my case, I lost my eighteen year-old daughter Emily after she consumed one OxyContin pill given to her by a relative. Others in our group are struggling with an addicted family member; the majority of these cases began due to an injury that led to an opioid prescription.

ARPO will comment on two aspects to the Draft Blueprint. First, we will comment on the broader Long-Acting/Extended-Release Opioid Class-Wide Risk Evaluation and Mitigation Strategy (LA/ER Opioid REMS) that the FDA has designed, of which the education of prescribers (addressed in this Draft Blueprint) and patients is said to be the central component. Second, we will address the specific elements included in the Draft Blueprint.

FDA’s Opioid REMS
ARPO takes issue with several key aspects to the FDA’s LA/ER Opioid REMS. First, it holds prescriber and patient education as the primary element of the REMS. Many of our individual members were extensively involved in the meetings that were held by FDA to consider the LA/ER Opioid REMS, and we strongly advised FDA not to restrict the LA/ER Opioid REMS to solely educational measures (e.g. see May 27, 2009 statement of Dr. Kirk Van Rooyan and
July 5, 2010 statement of Peter W. Jackson). Several FDA Advisory Committee members advised against this sole focus on education as well. FDA has failed miserably at addressing the opioid crisis because of its steadfast refusal to address the oversupply of these drugs. It is tragic that many more people must die because of FDA’s refusal to admit that it has been wrong on this point. The CDC graphic below tells the story as well as any words can.

Rates of prescription painkiller sales, deaths and substance abuse treatment admissions (1999-2010).

![Diagram showing rates of prescription painkiller sales, deaths, and substance abuse treatment admissions (1999-2010).]

According to the FDA website, while these terrible trends were ongoing, Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research, was leading the “Pharmaceutical Quality for the 21st Century Initiative, FDA’s highly successful effort to modernize drug manufacturing and its regulation,” for which she is roundly praised. Where is the accountability for the tragic results in the above figure? How can someone in her position keep their job with these results?

Second, the prescriber education element of FDA’s LA/ER Opioid REMS is seriously flawed as it provides that prescriber education is merely optional. Once again, many experts, including a number of FDA’s own Advisory Committee panelists, advised against an optional approach (e.g.

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1 For example, see July 23, 2010 Opioid REMS AC Committee transcript: Dr. Markman 157-158; Dr. Berger 169; Dr. Gray 176-177; Dr. Vaida 180-181.
see testimony of Dr. Nathaniel Katz, July 23, 2010). This weak and timid proposal is shocking after all the deaths.

Third, while the REMS notification letter to the drug companies indicated that it was FDA’s “expectation” that the prescriber education program would be conducted by accredited, independent continuing education (CE) providers, there is no specification that the actual content of the training curriculum must be developed independently of drug company influence. There is nothing to prevent a drug company from supplementing the content contained in the Draft Blueprint with any manner of additional content related to the use of its product. This is especially true given that the CE providers will be working for the drug companies and will in fact be compensated by them through unrestricted grants. The fact that the drug companies have identified a need for 30 hours or more of education is a further confirmation that the content to be provided by them will extend far beyond the core curriculum of the FDA Blueprint.

FDA’s failure to require the development and delivery of a truly independent prescriber education program results in a lack of credibility of the training program. On the FDA Opioid REMS website is a table that identifies all of the companies that produce the LA/ER opioids subject to this LA/ER Opioid REMS. Many of these companies have been convicted and fined for illegality related to marketing of their drug products. For example: in 2007 Purdue Pharma was fined $700 million for misbranding OxyContin “with the intent to defraud and mislead”. In 2009 King Pharmaceuticals (now Pfizer) was fined $1.2 billion for off-label marketing. In 2010 Roxanne was fined $280 million for false pricing in order to extract more money from federal healthcare programs, and in that same year Ortho McNeil Janssen was fined $75 million for off-label marketing of Topamax. In 2011 Actavis was fined $170 million for Medicaid fraud. Clearly, deceit and unethical marketing have characterized the way that these companies do business. The history of reprehensible illegalities in the marketing of drugs by the companies

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2 "Since I chaired the first opioid risk management meeting, now eight and a half years ago, somewhere approaching 100,000 people have died of prescription opioid overdoses and related events. What have we been doing all this time? Innumerable forms of voluntary education, monitoring, and surveillance, the essence of the current FDA and IWG proposals. You just sat through a day of presentations describing the results of these approaches. Do you really need any more data to tell you that voluntary education does not work? I will remind you of the definition of insanity, attributed to Albert Einstein, doing the same thing over and over again, and expecting the results to be different.”

3 See testimony of Cynthia Kear, California Academy of Family Physicians, July 23, 2010: “effective education, whether funded by government and/or industry, must include accredited educational providers operating within today’s widely accepted industry standards. Beyond effectiveness, this is the case if that education is to be perceived as credible, both by prescribers as well as by the larger community. Current medical education industry standards provide clear guidelines about the need to establish firewalls between pharmaceutical companies and the prescribers who use their therapeutic agents.” Also, Dr. Art Van Zee, July 23, 2010: “I also have great concerns about the current proposal for the industry to provide REMS education to physicians regarding opioid use. It was the industry’s blurring of promotion, marketing, and education that played a major role over the last decade in the prescription opioid problem...”

4 http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm251735.htm
that produce LA/ER opioids proves that no credible education program can rely upon these companies for substantive support given what we now know about their conduct.

The provisions of the Food and Drug Administration Amendments Act of 2007 ("FDAAA") related to prescriber training read as follows:

"The elements to assure safe use....may require that:
(A) Health care providers who prescribe the drug have particular training or experience, or are specially certified (the opportunity to obtain such training or certification with respect to the drug shall be in a widely available training or certification method including an on-line course or via mail) as approved by the Secretary at reasonable cost to the provider;"

This language clearly indicates that the FDA "may require" that prescribers complete the training. There is nothing in the above language that compels FDA to offer merely voluntary training. There is also no mention in the above language that the drug companies must be allowed to participate in the development of the prescriber education curriculum.

FDA has also had the authority to review evidence in support of a change in the prescribing indications for previously-approved LA/ER opioids (GAO 2006), and in fact FDA has even removed a number of drugs from the market for safety-related reasons. FDAAA gave FDA even more authority to consider evidence in support of a needed change in the medical indications for the opioids:

"The elements to assure safe use....may require that:
(D) the drug be dispensed to patients with evidence or other documentation of safe-use conditions, such as laboratory test results;"

FDA's failure to take advantage of the flexibility built into the FDAAA defies logic. The Congress handed FDA a tool by which it could address the national epidemic of opioid addiction and death documented in the graph above. Instead, FDA simply took a pass on developing any strong measures to address the problems of liberal prescribing indications not supported by evidence-based research and the resulting oversupply/overavailability which is driving the epidemic. An FDA LA/ER Opioid REMS which similarly omits this critical component is seriously incomplete and almost certain to be ineffective.

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5 During the July 2010 AC Committee meeting there was some discussion about linking mandatory prescriber training to the DEA registration process, which according to FDA may require legislation.
Specific Elements in the Draft Blueprint
Under Section I, add the following bullet:
  • Don’t stock patients’ medicine cabinets with unused opioids.

Under Section IIa, add the following bullets:
  • Risk of diversion due to unused medication and ease of access.
  • Risk of misuse due to widespread misperception that an FDA-approved, doctor-prescribed product is safe.

Under Section IIb, add the following bullet:
  • Don’t initiate opioid therapy before considering safer alternatives, such as primary disease management, cognitive-behavioral therapy, physical therapy, non-opioid analgesics and exercise.

Under Section IIb, revise the second bullet inserting the following after “psychosocial factors”: “such as depression and other psychiatric disorders”.

Under Section IIc, add the following sentence: “Don’t prescribe LA/ER opioids to opioid-naïve patients.”

Section V: add the following statement: “Prescribers should explain that opioids are for time-limited use.”

Section VI:
  • The paragraphs in this section go a,b,c,b,c,d.
  • Add the following new paragraph:
    “Evidence to support the use of LA/ER opioids for chronic noncancer pain (CNCP) is weak. Use of LA/ER opioids to treat CNCP should always be considered a last resort given the increased risk of addiction, hyperalgesia, and reduced efficacy over time.”
  • Add the following sentence at the end of the second “c”:
    “Please note that risks of addiction, death from respiratory depression, etc. from LA/ER opioids remain when the product is swallowed whole.”

ARPO recommends that the FDA include in its Draft Blueprint the “Cautious, Evidence-based Opioid Prescribing” publication included on the website of Physicians for Responsible Opioid Prescribing at the following link:
http://www.responsibleopioidprescribing.org/index_9_2167612031.pdf
Conclusion and Recommendations

In conclusion, FDA has proposed an LA/ER Opioid REMS that will be ineffective at addressing what is widely-acknowledged by its own experts to be a major public health problem because it is voluntary and lacks credibility due to the intentional involvement of the drug companies. Even more important, the proposed LA/ER Opioid REMS is very narrow: prescriber education is but one element of a broader array of strategies that must be implemented in order to meaningfully address the opioid problem. In August of this year, FDA received a letter from several members of Congress which stated as follows:

“At present, labels on most opioids have non-specific indications that simply list ‘moderate to severe pain’. Evidence suggests that benefits may outweigh risks when opioids are used short-term for acute pain and when used at the end of life to treat cancer pain. However, evidence to support long-term use of opioids for chronic noncancer pain (CNCP) is lacking. In fact, many experts believe that the practice of treating CNCP with opioids may actually harm more people than it helps. An expert review of the scientific evidence would help clarify appropriate indications and provide for safer use of these powerful medications.”

ARPO concurs with this recommendation and offers the following recommendations:

1) Make the prescriber education mandatory and make development and implementation independent of drug company influence;
2) Enhance the LA/ER Opioid REMS proposal by adding these additional elements:
   a) dispensing only in certain healthcare settings so certain prescribers can’t prescribe Schedule II opioids;
   b) pharmacist training;
   c) mandatory patient counseling by prescriber and pharmacist that explains risks of respiratory depression, addiction with long-term use, and heroin-like properties, and that requires patient signature upon each receipt of dispensed opioid medication;
   d) mandatory labeling cautions on all opioid pill containers; and
3) FDA must use its authority to hold a review of the evidence supporting the current prescribing indications as requested by Congressional members.

Sincerely,

\[Signature\]
Peter W. Jackson, President
Advocates for the Reform of Prescription Opioids
www.rxreform.org