PHARMACEUTICAL MANUFACTURING RESEARCH SERVICES, INC.

August 25, 2016

**Via Electronic Submission**

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. FDA-2016-P-0645

Dear Ms. Bennett,

Thank you for your letter dated August 16, 2016 in which you respond to my Citizen Petition received on February 22, 2016, Docket No. FDA-2016-P-0645. In your letter you correctly recognize my request. Your letter states "Your petition requests that the Agency require specific studies to support abuse-deterrent labeling, revise FDA guidance to remove certain types of abuse-deterrent studies, and require all opioid drugs with approved abuse-deterrent labeling to meet certain standards, and if they do not meet those standards, revise the labeling to remove the abuse-deterrent labeling claims. Specifically with respect to reformulated OxyContin, your petition also requests that the Agency remove the abuse-deterrent labeling claims, revoke the three-year exclusivity awarded to Purdue Pharma L.P. for reformulated OxyContin, and 'restore NDA No. 020553 for original OxyContin.'"[1]

I appreciate that your response acknowledges the complexity of the issues raised. Your letter states that the "FDA has been unable to reach a decision on your petition because it raises complex issues requiring extensive review and analysis by Agency officials. This interim response is provided in accordance with FDA regulations on citizen petitions (21 CFR 10.30(e)(2)). We will respond to your petition as soon as we have reached a decision on your request."[2]

I wish to remind you that there is currently an (iatrogenic) opioid epidemic in the United States and in 2014 more than 28,000 persons died from an opioid overdose that is largely due to prescription drugs that were approved by the FDA. Each and every day there will be an additional 76 deaths and that number continues to grow. Since submitting my Citizen Petition 188 days has elapsed, resulting in an additional 14,000+ deaths. The FDA must have a sense of urgency and take action as quickly as possible.

[1] CDER Interim Response Letter to Pharmaceutical Manufacturing Research Services Inc., Aug 16 2016.
[2] Ibid.

The Federal Food, Drug and Cosmetic Act vests the FDA with the regulatory authority and responsibility for ensuring the safety of all marketed medical products. The Act is a safety statute whose primary objective is the protection of public health and the FDA has a duty to protect the public welfare, health and safety. That duty includes having substantial evidence that a drug is safe to use under the conditions or use prescribed, recommended, or suggested in the labeling. Labeling OxyContin as abuse deterrent does not meet such standard. The Act prohibits the introduction into interstate commerce of any drug that is misbranded, "a drug shall be deemed to be misbranded if its labeling is false or misleading in any particular".[3] Under its current abuse deterrent labeling, OxyContin is misbranded.

The FDA is required to have clarity in its actions. Because of the acknowledged complexity of the issues raised in my Citizen Petition the FDA must make a decision in favor of the public health, welfare and safety. This means that the FDA must remove the abuse deterrent labeling from OxyContin. The FDA has clear scientific, medical, and legal evidence supporting the removal of abuse deterrent labeling from the OxyContin labeling and should do so immediately given the substantial evidence that OxyContin in its present formulation is not abuse deterrent.

My Citizen Petition included redacted information and made reference to video evidence demonstrating the ease of abuse of OxyContin. My Citizen Petition was received on February 22, 2016. For six months the FDA has not asked me to provide the redacted information or to view the video. If the veracity of the science supporting the Citizen Petition is unquestioned, why has the FDA delayed action?

This is not the first time that the FDA has labeled OxyContin with abuse deterrent labeling and then had to withdraw the labeling. In 1995 the FDA approved OxyContin for acute pain with abuse deterrent labeling "delayed absorption, as provided by OxyContin tablets is believed to reduce the abuse liability of a drug."[4] Mistakenly, the FDA approved this labeling on a belief rather than on substantial evidence, as required. The FDA stated that "it was initially believed that the PK characteristics of a CR formulation would reduce the reinforcing properties."[5] This mistaken belief also led to the approval of an 80mg and 160mg tablet and accelerated the opioid epidemic. In 2000 there was widespread media and state reports of OxyContin abuse and diversion (which contributed to the 160 mg version being withdrawn from the market). In August 2001 the FDA deleted the language regarding reduced abuse liability with the CR formulation. History has repeated itself again in April of 2013. In April 2013 the FDA, without substantial evidence, relabeled OxyContin with abuse deterrent labeling and should again remove this abuse deterrent labeling.

As detailed in my Citizen Petition, there are clear, compelling, and cumulative reasons to remove OxyContin abuse deterrent labeling. First, OxyContin abuse deterrent labeling was approved as a supplement to reformulated OxyContin based upon one and only one liking study, OTR1018.

[3] Federal Food, Drug, and Cosmetic Act, Sec. 502 [352].
[4] FDA Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committees, November 13 & 14, 2008.
[5] Ibid.



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In the FDA's own words, "no other data exists to support approval of this supplement."[6] Furthermore, in liking study OTR1018 the FDA used only pharmacodynamic data to approve abuse deterrent labeling for OxyContin. This pharmacodynamic data did not reach the required "meaningful statistical analysis"[7] cited in the FDA's Guidance. The OxyContin labeling states: "The intranasal administration of finely crushed OxyContin was associated with a NUMERICALLY lower mean and median drug liking score and a lower mean and median score for take drug again, compared to finely crushed original OxyContin or powdered oxycodone HCl as summarized in Table 4."[8] [emphasis added].

Also, pharmacokinetic data should have been required, and pharmacokinetic and pharmacodynamic data must correlate to be reproducible, and scientifically rigorous. Pharmacokinetic data is valid data and reproducible. In multiple open FDA DAAAP Advisory Committee meetings it has been stated that pharmacokinetic and pharmacodynamic data from liking studies do not correlate. Therefore, pharmacodynamic data generated by liking studies are not reproducible, valid scientific evidence and cannot be used to approve abuse deterrent labeling. In Table 4, patients liked finely crushed original OxyContin over oxycodone HCl powder. For subjects participating in an oxycodone HCl abuse study, the highest level of liking should have been with oxycodone HCl powder, but in the pivotal study to approve abuse deterrent labeling for OxyContin, the subjects liked finely crushed original OxyContin over oxycodone HCl powder. This liking study design is flawed and this study is flawed.

This single study OTR1018 is the reason OxyContin was given abuse deterrent labeling and has enabled Purdue sales representatives to give hundreds of thousands of presentations to doctors to prescribe OxyContin with a margin of safety. Because of its FDA approved abuse deterrent labeling, Purdue's OxyContin has improperly received three years of FDA exclusivity from competition, and the FDA has removed the original OxyContin NDA for safety reasons, which prevents generic products from providing tens of billions of dollars of savings to consumers in pain.

Second, abuse deterrent labeled OxyContin provides no meaningful abuse deterrence to the primary known route of abuse, oral consumption. The FDA has stated that "the vast majority of deaths associated with OC (original OxyContin) were related to oral consumption."[9] The approved labeling for OxyContin, what sales representatives are promoting to doctors, states "relative to original OxyContin, there is an increase in the ability of OxyContin to resist crushing, breaking, and dissolution using a variety of tools and solvents."[10]

This statement is true, but highly deceptive, clearly lacks full disclosure, and is misleading. OxyContin's labeling, in Table 4, reports that both original OxyContin and reformulated OxyContin are finely crushed, overcoming the resistance to crushing and breaking. Also, it was

[6] FDA Reference ID: 3712567, p. 4-5.
[7] "Abuse-Deterrent Opioids Evaluation and Labeling Guidance for Industry" published April 2015, p. 4.
[8] OxyContin® Package Insert 9.2, p. 24.
[9] FDA Reference ID: 3258740, p. 4-5.
[10] OxyContin® Package Insert 9.2, *In Vitro Testing*.



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reported by the FDA that reformulated OxyContin when vigorously chewed, dose dumps. The FDA review reported "upon chewing vigorously, OFR and OC products are bioequivalent with respect to oxycodone Cmax and AUC."[11] Reformulated OxyContin has no meaningful advantage in breaking or crushing over original OxyContin. The "Summary of Evidence and Conclusions section of the FDA reformulated OxyContin clinical review included the statement, "The controlled-release properties of ORF (reformulated OxyContin) can be overcome with chewing and swallowing."[12] Physicians should have been informed that the controlled-release properties of OxyContin can be overcome when finely ground and swallowed and chewed vigorously and swallowed. This is more important information to a physician than the information in the labeling. This information would prohibit rather than approve abuse deterrent labeling for OxyContin.

Third, the OxyContin label informs physicians that "when subjected to an aqueous environment, OxyContin gradually forms a viscous hydrogel (for example a gelatinous mass) that resists passage through a needle."[13] The Division Director of DAAAP, Robert A. Rappaport, MD in his summary review stated: "These features also render the product almost impossible to dissolve, syringe, and inject."[14] Douglas Throckmorton, MD in his summary review stated: "OCR gradually forms a viscous hydrogel (i.e. a gelatinous mass) that resists passage through a needle. The in vitro testing was sufficient to demonstrate that OCR (reformulated OxyContin) prevents oxycodone from being drawn into a syringe to any meaningful extent."[15] These statements are incorrect and misleading. The fact is that when OxyContin is subjected to an aqueous environment it can easily be extracted to high purity and high label claim by an unskilled person in minutes, with a viscosity similar to water, drawn into a syringe and prepared for injection. OxyContin can also be extracted in a common solvent to high purity and high label claim, by an unskilled person and easily drawn into a syringe or converted into crystalline form for distribution and sale. Reformulated OxyContin does not have any meaningful abuse deterrent properties to prevent extraction and injection.

Under the Federal Food, Drug and Cosmetic Act OxyContin is "misbranded" within the meaning of the Act. Information contained in the drug's labeling pertains not only to misleading affirmative claims, but also to material omissions as well. The labeling fails to fully disclose potential risks for prescribing OxyContin. The FDA will be acting within its mandate, as well as the public interest, by granting this Petition. The enclosed information requires the FDA Commissioner to expeditiously grant the actions requested in my Citizen Petition, Docket No. FDA-2016-P-0645.

[11] FDA Reference ID: 3190167, p. 10.
[12] FDA Reference ID: 3258740, p. 3.
[13] OxyContin® Package Insert 9.2, *In Vitro Testing*.
[14] FDA Reference ID: 3258740, p. 1.
[15] FDA Reference ID: 3294145, p. 9.



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Sincerely,

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