November 13, 2018

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

CITIZEN PETITION

The undersigned, on behalf of Pharmaceutical Manufacturing Research Services, Inc. ("PMRS"), submits this petition pursuant to 21 C.F.R. §§ 10.30 and 10.31, and Section 505(q) and other provisions of the Federal Food, Drug, and Cosmetic Act ("FD&C Act"). PMRS requests that the Food and Drug Administration ("FDA") refrain from approving any pending or future application for an opioid product submitted pursuant to section 505(b) or 505(j) of the FD&C Act, including NDA No. 209774 submitted by SpecGx LLC ("MNK-812"), with an indication or any other labeling that suggests that the product is appropriate for chronic use. PMRS further requests that FDA refrain from approving any pending or future application for an opioid product with abuse-deterrent labeling submitted pursuant to section 505(b) or 505(j) of the FD&C Act, including NDA No. 209774 submitted by SpecGx LLC, absent a meaningful demonstration of any such claims in compliance with a defined legal standard rather than mere reliance on methods unlawfully prescribed in the form of an FDA Guidance Document.

ACTION REQUESTED

To protect the public health interest in ensuring the responsible prescribing and use of opioid drug products, PMRS respectfully requests that the FDA take the following actions:

- Refrain from approving any pending or future application for an opioid product submitted pursuant to section 505(b) or 505(j) of the FD&C Act, including NDA No. 209774 submitted by SpecGx LLC, with an indication or any other labeling which allows for administration for control of chronic pain.

- Refrain from approving any pending or future application for an opioid product submitted pursuant to section 505(b)(2) or 505(j) of the FD&C Act, including NDA

No. 209774 submitted by SpecGx LLC, that relies upon Roxicodone as the Reference Listed Drug (RLD) to support efficacy for the treatment of chronic pain.

- Refrain from approving any pending or future application for an opioid product with abuse-deterrent labeling submitted pursuant to section 505(b) or 505(j) of the FD&C Act, including NDA No. 209774 submitted by SpecGx LLC, absent a meaningful demonstration of any such claims in compliance with a defined legal standard rather than mere reliance on methods unlawfully prescribed in the form of an FDA Guidance Document.

A. STATEMENT OF GROUNDS

I. Refrain from approving any pending or future application for an opioid product submitted pursuant to section 505(b) or 505(j) of the FD&C Act, including NDA No. 209774 submitted by SpecGx LLC, with an indication or any other labeling which allows for administration for control of chronic pain.

If MNK-812 is approved with an indication that includes control of chronic pain, it would be misbranded and its presence on the market would negatively affect the public health, potentially further fueling the current epidemic of opioid addiction.

For the reasons discussed herein, such labeling would be false and misleading, and lacks "substantial evidence consisting of adequate and well-controlled investigations" that the drug will have the effects it purports or is represented to have in the label as required by the FD&C Act.[1]

The FDA defines chronic pain as "either pain persisting for longer than 1 month beyond resolution of the underlying insult, or pain persisting beyond 3 months."[2] However, as PMRS has articulated in a previously-filed Citizen Petition (FDA-2017-P-1359), beginning with the approval of original OxyContin in 1995, the Agency has unlawfully allowed opioids to be marketed with chronic-use labeling, despite a lack of evidence to support the chronic-use indication.[3] Even today, there remains a lack of evidence that prescription opioids are effective or safe therapeutics in the chronic pain setting.[4] Continuing to label opioid drug products for chronic treatment is a violation of sound public policy.

The risks of FDA's approval of opioid drug products for chronic treatment of pain are recognized by providers and pain researchers. As summarized by Dr. Jane C. Ballantyne, M.D., F.R.C.A., Department of Anesthesiology and Pain Medicine, University of Washington:

> "Opioid analgesics have been used increasingly over the past 20 years for the management of chronic non-cancer pain in the USA under the assumption that they were

[1] 21 U.S.C. 355(d)
[2] FDA, *Guidance for Industry—Analgesic Indications: Developing Drug and Biological Products*, February 2014, p. 2 (emphasis added), accessed on November 13, 2018 from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM384691.pdf
[3] PMRS, Citizen Petition, Docket No. FDA-2017-P-1359 (Mar. 6, 2017)
[4] *See, e.g.*, FDA, Transcript, *Assessment of Analgesic Treatment of Chronic Pain: A Scientific Workshop* (May 31, 2012), pp. 7-8 (statement of Janet Woodcock, M.D., Director, CDER) (commenting that, although the evidence base is strong for the efficacy of opioids for up to 12 weeks of treatment, their performance and liabilities beyond 12 weeks have not been demonstrated "in the type of evidentiary base that FDA usually has for approval for when [the Agency] grant[s] an indication"), accessed November 13, 2018 from https://www.regulations.gov/contentStreamer?documentId=FDA-2012-N-0067-0017&attachmentNumber=2&contentType=pdf

> safe and effective when used as directed. The accuracy of that assumption has not been tested against accumulated evidence. The safety of opioids used on a long-term basis has not been tested in clinical trials. Epidemiologic evidence from examinations of such use in the general population indicates that the risk of overdose increases in a dose–response manner. Such evidence also suggests increased risk of fractures and acute myocardial infarctions among elderly users of opioids for chronic pain. Experimental evidence supports short-term use of opioids, but trials of long-term use for chronic pain have not been conducted."[5]

The dangers of this assumption are clear. In the words of Dr. Daniel Clauw, M.D., Director, Chronic Pain and Fatigue Research Center; Professor of Anesthesiology, Medicine (Rheumatology) and Psychiatry, University of Michigan:

> "What bothers me moreso as one of the world's leading pain researchers are the large numbers of patients taking opioids in the United States for chronic pain that think that the opioids are helping their pain, but when we look at them as a physician, as a sort of neutral third party, we actually think the opioids are harming them more than they're helping them, but that patient believes, because the opioids did help them the first couple of months that they went on the opioid, that patient continues to believe that the opioids are helping them even though we don't see any evidence of this."[6]

Yet, under the FD&C Act, drugs are not approved and labeled by FDA on the basis of assumptions. The statutes and regulations that confer FDA's authority to approve drug products clearly require the Agency to have substantial evidence of a drug's efficacy before that product can be lawfully approved. In recent remarks made as a member of the Pain Management Best Practices Inter-Agency Task Force on May 31, 2018, Dr. Clauw continues:

> "Those of us who do a lot of clinical trials in pain, and I'm sure Sharon [Hertz, Director of FDA Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)] would agree with me. I have never done a clinical trial in pain—and I've done a lot of them—where the magnitude of the incremental benefit you get with the active treatment is more

[5] Jane C. Ballantyne, "Safe and effective when used as directed": the case of chronic use of opioid analgesics, 8 J Med Toxicol. 417, 417 (2012), accessed November 13, 2018 from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3550253/pdf/13181_2012_Article_257.pdf

[6] Daniel J. Clauw M.D, *Chronic Pain - Is it All in Their Head?*, published August 16, 2017. Accessed November 13, 2018 from https://www.youtube.com/watch?v=B0EhNajqkdU&t=1h13m22s

than the placebo effect. The placebo effect in every pain trial exceeds the incremental benefit that you see with the active treatment."[7]

Put simply, even today, there remain no adequate clinical studies that provide substantial evidence that opioids are an effective therapy for the treatment of chronic pain.

In this regard, FDA's approval of OxyContin provides an instructive example. In 1995, the FDA approved OxyContin 10 mg, 20 mg, and 40 mg tablets (NDA 20-553) using a single clinical trial comparing 10 mg, 20 mg and placebo as substantial evidence of efficacy. As documented in the FDA Medical Officer's Review, completed in June 1995 by Dr. Curtis Wright and reviewed by Dr. Douglas Kramer, Dr. Wright states, "Oxycodone 20 mg separated from placebo within a week with an effect size of about 0.4/0.6 or 2/3 SD. **The 10 mg was not effective**, but provided information as a half-dose dose control. This data is not adequate by itself to support an OA indication, but is a very helpful trial in a non-oncologic chronic pain model." (emphasis added)[8]

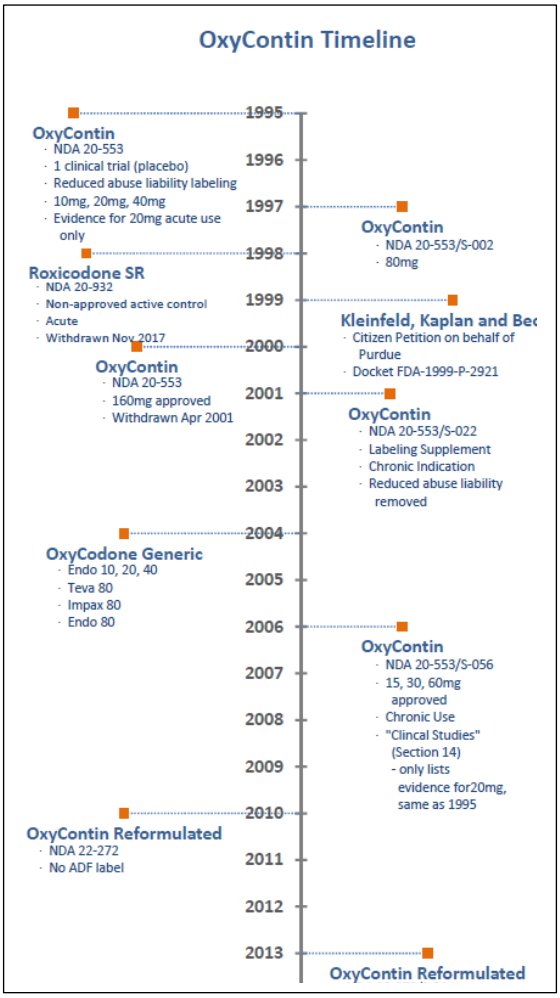


Figure 1 — OxyContin Approval Timeline

Section 14 (Clinical Studies) of OxyContin's package insert reiterates this conclusion: "A double-blind, placebo-controlled, fixed-dose, parallel group, two-week study was conducted in 133 patients with persistent, moderate to severe pain, who were judged as having inadequate pain control with their current therapy. In this study, OXYCONTIN 20mg, **but not 10mg**, was statistically significant in pain reduction compared with placebo." (emphasis added). In this lone clinical study, OxyContin 10mg was not effective and OxyContin 40mg was not studied, yet 10mg and 40mg OxyContin tablets were approved. Thus, FDA exceeded its statutory authority

[7] HHS, *PMTF Day 2 pt 2 Clinical Topic Discussions*, published June 14, 2018. Accessed November 13, 2018 from https://www.youtube.com/watch?v=gVbThnebqQ0&t=29m30s

[8] U.S. Food and Drug Administration, Center for Drug Evaluation and Research. OxyContin NDA 20-533, *Medical Officer Review – OxyContin Study 1102-Non-Malignant Pain*, May 19, 1995, p. 92, Accessed November 13, 2018 from https://www.regulations.gov/contentStreamer?documentId=FDA-2018-N-1797-0011&attachmentNumber=6&contentType=pdf

in approving 10mg and 40mg absent substantial evidence of efficacy, and in the presence of evidence that OxyContin 10mg was not effective.

The facts are clear:

- Six clinical studies were conducted and submitted for FDA approval.
- Only 1 study (1102) was adequate and well-controlled and used to approve OxyContin.
- Study 1102 was a comparison of 10mg, 20mg and placebo for 14 days in osteoarthritis.
- In the FDA's own words, "10mg was not effective" in this study.
- 20mg provided "short-term analgesic efficacy".
- 40mg was not studied.
- "This data is not adequate by itself to support an OA indication, but is a very helpful trial in a non-oncologic chronic pain model."

This information is foundational for approval of all other strengths of OxyContin. All additional tablet strengths of OxyContin—15mg , 30mg, 60mg, 80mg, and 160mg—were approved as supplements to NDA 20-553 and likewise have not been demonstrated by substantial evidence to be effective.

Following approval, OxyContin was originally labelled "for the management of moderate to severe pain in patients where use of an opioid analgesic is indicated for more than a few days."[9] The OxyContin package insert also included the claim, "Delayed absorption, as provided by OxyContin tablets, **is believed to reduce the abuse liability of a drug**." (emphasis added)[10]

By 2000, the FDA reported on OxyContin abuse and the opioid epidemic. The FDA knew that OxyContin should not have been approved and the agency was at a crossroad—revoke the approval of OxyContin, or cover up the approval. The following excerpt is from a July 14, 2001 meeting between FDA and Purdue:

> "Dr. McCormick began the labeling discussion by expressing the Agency's concern about the clinical trials section. The trials currently in the label are pain "models" in artificial settings with regard to the appropriate use of the product. **The Agency's position is that neither the osteoarthritis, nor the single-dose post-operative pain study provide adequate data for a claim in the label. The studies, as they were**

[9] U.S. Food and Drug Administration, Center for Drug Evaluation and Research, NDA 20-553 *Approval*, Dec 12, 1995.
[10] Caitlin Esch, "How one sentence helped set off the opioid crisis", Marketplace. December 13, 2017. Accessed November 13, 2018 from https://www.marketplace.org/2017/12/13/health-care/uncertain-hour/opioid

> **performed and described in the label, are in contradiction to the indications we have inserted in the label.** The sponsor believes that, since the studies are placebo-controlled, they should be allowed to remain. Dr. McCormick stated that the studies must show separation of the study drug from placebo in the intended population and that the studies, which enrolled patients based solely on their disease state, rather than their pain status (and their use of and the failure of other non-opioid medications), send a misleading message regarding the appropriate use of the drug." (emphasis added)[11]

Thus, there is no question that OxyContin's approval should have been withdrawn in 2001.

However, instead of revoking OxyContin, and without any additional clinical data and knowing there was no evidence of efficacy beyond a single 14-day trial, the FDA decided in 2001 to revise the OxyContin label to include an indication for chronic treatment. The revised OxyContin labeling stated: "OxyContin is an opioid agonist product indicated for the management of pain severe enough to require daily, around-the-clock long-term opioid treatment and for which alternative treatment options are inadequate." Labeling OxyContin for chronic treatment (conclusions by FDA Division Director, Cynthia McCormick, MD, include "…access to this product by patients suffering with chronic pain and the prevention of collateral harm to the more widespread community by virtue of diversion and abuse."[12]) using a labeling supplement to NDA 20-553 with no new clinical data and justifying the change in labeling by "INDICATIONS were simplified to reinforce the appropriate patient population for whom this product is intended"[13] exceeds the statutory authority of the FDA. At the same time, the FDA justified removing the reduced abuse liability statement in the label, "Although it was initially believed that the PK characteristics of a CR formulation would reduce the reinforcing properties, experience has shown that defeat of the CR mechanisms is associated with abuse."[14] The FDA admitted that it was approving labeling on "belief" rather than substantial evidence and was forced to reverse their decision in light of the growing epidemic. Thus, the regulatory history of

[11] U.S. Food and Drug Administration, Center for Drug Evaluation and Research. OxyContin NDA 20-533, June 14, 2001 Meeting Minutes. Accessed November 13, 2018 from https://www.regulations.gov/contentStreamer?documentId=FDA-2018-N-1797-0011&attachmentNumber=3&contentType=pdf

[12] U.S. Food and Drug Administration, Center for Drug Evaluation and Research. OxyContin NDA 20-533, S-022 *Administrative Document: Division Director's Review of Labeling Supplement and Basis for Action*, July 16, 2001, p. 5, accessed November 13, 2018 from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/020553_S022_OXYCONTIN_AP.pdf

[13] *Id*. at p. 2.

[14] "History of OxyContin: Labeling and Risk Management Program", FDA Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committees, Nov. 13-14, 2008, p. 9, accessed November 13, 2018 from http://wayback.archive-it.org/7993/20180126135807/https://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4395s1-05-FDA-Shibuya.ppt

OxyContin indicates that FDA did not have substantial evidence of efficacy, as required by law, when it decided to approve labeling for the treatment of chronic pain. Furthermore, for all the approved strengths of OxyContin—10mg, 15mg, 20mg, 30mg, 40mg, 60mg, 80mg, and at one time 160mg—there is no evidence for efficacy for any strength other than the 20mg dose, and then only in a limited osteoarthritis study for short-term analgesia.

Indeed, the lack of evidence to support the efficacy of prescription opioids in the treatment of chronic pain has also been recognized by the Centers for Disease Control and Prevention (CDC). In its March 2016 *Guideline for Prescribing Opioids for Chronic Pain*, the CDC acknowledged that: "[T]he guideline uses the best available scientific data to provide information and recommendations to support patients and clinicians in balancing the risks of addiction and overdose with the limited evidence of benefits of opioids for the treatment of chronic pain."[15] The CDC Guideline is the culmination of almost three years of work by the world's experts in epidemiology.[16] The Guideline is the ultimate authority on the opioid epidemic, having combined the resources and knowledge of top experts in the field, numerous rigorous studies, and a multitude of panels. Some of the CDC's recommendations and conclusions in the Guideline include:

> "The evidence reviews forming the basis of this guideline clearly illustrate that there is much yet to be learned about the effectiveness, safety, and economic efficiency of long-term opioid therapy."[17]
>
> "Most placebo-controlled, randomized trials of opioids have lasted 6 weeks or less, and we are aware of no study that has compared opioid therapy with other treatments in terms of long-term (more than 1 year) outcomes related to pain, function, or quality of life. The few randomized trials to evaluate opioid efficacy for longer than 6 weeks had consistently poor results."[18]
>
> "The science of opioids for chronic pain is clear: for the vast majority of patients, the known, serious, and too-often-fatal risks far outweigh the unproven and transient benefits."[19]

[15] Thomas R. Frieden, M.D., M.P.H., and Debra Houry, M.D., M.P.H, *Reducing the Risks of Relief — The CDC Opioid-Prescribing Guideline*, N Engl J Med, April 21, 2016, p. 1501, accessed November 13, 2018 from http://www.nejm.org/doi/pdf/10.1056/NEJMp1515917
[16] Dowell D, Haegerich TM, Chou R. *CDC Guideline for Prescribing Opioids for Chronic Pain* — United States, 2016. MMWR Recomm Rep 2016;65(No. RR-1):1–49, p. 34 accessed November 13, 2018 from https://www.cdc.gov/mmwr/volumes/65/rr/pdfs/rr6501e1.pdf
[17] *See* n. *16* at 34.
[18] *See* n. *15* at 1501.
[19] *Id.* at 1503.

The FDA itself has also acknowledged the lack of evidence for the treatment of chronic pain using opioids in the context of the CDC Guideline. A special report published in The New England Journal of Medicine on April 14, 2016 and authored by then-current FDA Commissioner Robert M. Califf, M.D., along with CDER Director Janet Woodcock, M.D., and Stephen Ostroff, M.D., commented:

> "The FDA does its best work when high-quality scientific evidence is available to assess the risks and benefits of intended uses of medical products. **Unfortunately, the field of chronic pain treatment is strikingly deficient in such evidence.** A key lesson learned during the development of the CDC guideline is that there is very little research on the long-term benefits of opioids for treating chronic pain. There is, however, growing evidence of harms associated with such use, and of the benefits of other nonopioid treatment alternatives." (emphasis added)[20]

Then-director of the CDC, Dr. Thomas Frieden, M.D., M.P.H., and Debra Houry, M.D., M.P.H., writing in The New England Journal of Medicine on April 21, 2016, clearly state the key issue, and the direct consequence on public health:

> "Whereas the benefits of opioids for chronic pain remain uncertain, the risks of addiction and overdose are clear."[21]

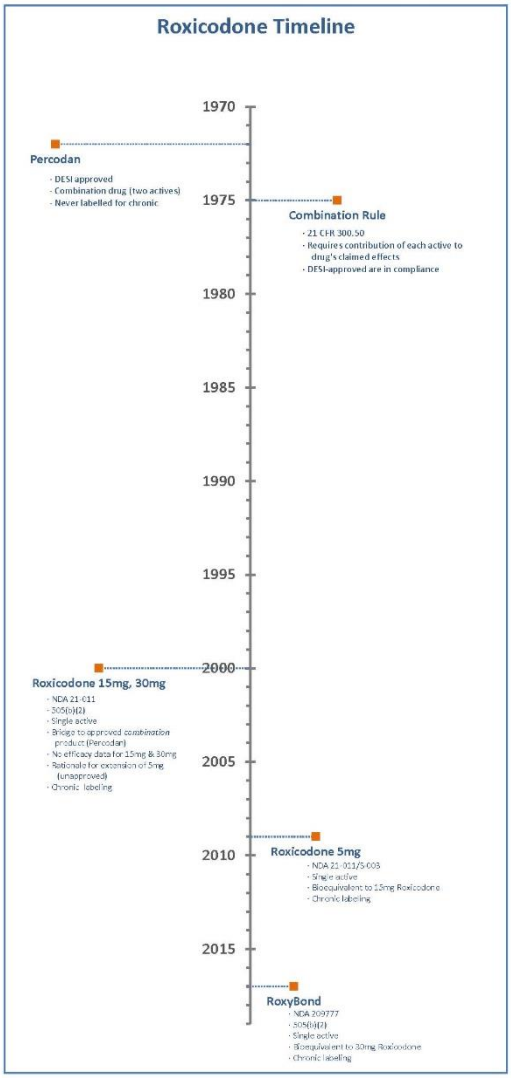
> "We know of no other medication routinely used for nonfatal conditions that kills patients so frequently."[22]

Thus, FDA's labeling of opioids for chronic use overturned decades of common medical teaching, which advised that prescription opioids "should be avoided when treating chronic pain."[23] Further, and in clear violation of its statutory authority, FDA approved these opioids for use in the treatment of chronic pain despite a lack of evidence supporting their efficacy for this use. This is the root cause of the opioid epidemic.

[20] Robert M. Califf et al., *A Proactive Response to Prescription Opioid Abuse*, 374 N Engl J Med. p. 1484 (2016) , accessed November 13, 2018 from http://www.nejm.org/doi/full/10.1056/NEJMsr1601307
[21] See n. 15 at 1502.
[22] *Id.* at 1503.
[23] See n.5.

II. Refrain from approving any pending or future application for an opioid product submitted pursuant to section 505(b)(2) or 505(j) of the FD&C Act, including NDA No. 209774 submitted by SpecGx LLC, that relies upon Roxicodone as the Reference Listed Drug (RLD) to support efficacy for the treatment of chronic pain.

FDA's committee background memo indicates that MNK-812's safety and efficacy "is based on demonstration of bioequivalence to the approved drug Roxicodone (oxycodone hydrochloride immediate-release tablets; NDA 021011)."[24]



Roxicodone has critical deficiencies concerning efficacy. As PMRS previously explained in Docket FDA-2018-N-0188, Roxicodone 15mg and 30mg tablets were illegally approved and illegally labelled for chronic treatment of pain.[25]

The FDA exceeded its statutory authority in approving Roxicodone 15mg and 30mg tablets (NDA 21-011) in 2000. Roxicodone—a single active ingredient tablet—was approved using Percodan—a multiple active ingredient product (oxycodone 5mg and 325mg aspirin) that was approved by DESI review—as the Reference Listed Drug (RLD).

Enacted in 1975, the "combination rule" 21 C.F.R. §300.50 requires contribution of **each** active ingredient to the drug's claimed effects. 21 C.F.R. §300.50 also clarified that DESI-approved products are in compliance with this rule. Due to this combination effect, Percodan, being a multiple active ingredient product, is a scientifically invalid choice of RLD for a single active ingredient product, such as Roxicodone. In such a scenario, it would be impossible to isolate the

[24] U.S. Food and Drug Administration, Center for Drug Evaluation and Research. *FDA Briefing Document - Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee, November 14, 2018*. Accessed November 13, 2018 from https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM625472.pdf

[25] PMRS, Inc. *Re: Docket No. FDA-2018-N-0188*, April 11, 2018. Accessed November 13, 2018 from https://www.regulations.gov/contentStreamer?documentId=FDA-2018-N-0188-0009&attachmentNumber=1&contentType=pdf

efficacy and safety of oxycodone specifically from Percodan such that the data could be applied to a product without aspirin. The FDA was prohibited from approving Roxicodone 15mg and 30mg tablets using Percodan as the RLD, yet it still approved the product[26,27]. In further defiance of applicable law and regulations, the FDA labeled Roxicodone 15mg and 30mg tablets for the treatment of chronic pain, labeling that Percodan did not and does not have. Substantial evidence, consisting of adequate and well-controlled clinical trials, would be required to show that Roxicodone 15mg was more effective than Roxicodone 5mg (single-entity oxycodone; marketed for decades, although not approved until 2000) and 30mg was more effective than 15mg; otherwise patients should be treated with the lower dose known to be efficacious. The FDA exceeded its statutory authority under the FD&C Act in approving Roxicodone 15mg and 30mg tablets and adding chronic labeling.

Moreover, the labeling for Percodan states that a maximum of 12 tablets can be administered per day, which corresponds to a maximum daily dose of 60 mg of oxycodone.[28] Thus, neither the expanded chronic pain indication nor the high daily doses of oxycodone suggested in the Roxicodone labeling are supported by FDA's prior findings of general analgesic efficacy for Percodan.

Additionally, the FDA further exceeded its statutory authority in approving Roxicodone 5mg tablets (a previously unapproved, yet marketed product) as a supplement to the application (NDA 21-011/S-003) in 2009. Roxicodone 15mg was illegally approved and without evidence of efficacy as demonstrated in the above section. Roxicodone 5mg is also required under the FD&C Act under 505 (d) (5) to provide substantial evidence that the 1/3 lower dose is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling. Comparing 3 X 5mg Roxicodone tablets to 1 X 15mg Roxicodone tablet (RLD) for bioequivalence[29] does not provide substantial evidence of efficacy, and certainly not for a single-entity drug that was approved using a combination drug RLD. The FDA illegally approved Roxicodone 5mg tablets and also illegally added chronic labeling. Roxicodone cannot be used

[26] U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Roxicodone NDA 21-011 *Medical Reviews*, accessed November 13, 2018 from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-011_Roxicodone_Medr_P1.pdf and https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-011_Roxicodone_Medr_P2.pdf

[27] U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Roxicodone NDA 21-011 *Administrative Documents*, accessed November 13, 2018 from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-011_Roxicodone_Admindocs_P1.pdf and https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-011_Roxicodone_Admindocs_P2.pdf

[28] U.S. Food and Drug Administration, Labeling for Percodan, 12/2016, accessed November 13, 2018 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021011s006lbl.pdf

[29] U.S. Food and Drug Administration, *Roxicodone Label*, May 15 2009, accessed November 13, 2018 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021011s003lbl.pdf

as an RLD to either support the efficacy of MNK-812 or the efficacy of any other oxycodone product for treatment of chronic pain.

The MNK-812 application improperly relies on the approval of Roxicodone and, thus, is in violation of the FD&C Act. It cannot be lawfully approved.

III. Refrain from approving any pending or future application for an opioid product with abuse-deterrent labeling submitted pursuant to section 505(b) or 505(j) of the FD&C Act, including NDA No. 209774 submitted by SpecGx LLC, absent a meaningful demonstration of any such claims in compliance with a defined legal standard rather than mere reliance on methods unlawfully prescribed in the form of an FDA Guidance Document.

1. FDA's Methodology Fails to Comply with the "Substantial Evidence" Standard

FDA's current methodology for approval of so-called abuse-deterrent labeling for opioids does not satisfy the requisite statutory standard, is scientifically flawed, and results in false and misleading labeling. Such labeling gives a false sense of security as to any meaningful solution to the raging opioid epidemic.

The FD&C Act requires "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, **or suggested** in the labeling." (emphasis added)[30] For an opioid product formulated with abuse-deterrent properties to satisfy that standard, there must be substantial evidence that the product's formulation actually results in a meaningful reduction in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death. This evidence can only be established through post-market epidemiologic studies.

The FD&C Act defines "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."[31,32]

[30] 21 U.S.C. § 355(d)(5)
[31] 21 U.S.C. § 355(d).
[32] FDA's regulations set forth a detailed description and list of what constitutes "adequate and well-controlled". *See* 21 C.F.R. § 314.126.

CDER's Abuse-Deterrent Labeling Guidance recommends that sponsors conduct the following three categories of premarket studies to obtain abuse-deterrent labeling: 1) Laboratory-based in vitro manipulation and extraction studies (Category 1); 2) Pharmacokinetic studies (Category 2); and 3) Human abuse potential studies ("HAP studies") (Category 3).[33,34]

Instead of providing evidence of an actual reduction in abuse potential, such premarket studies are intended to evaluate whether an opioid product's formulation can be "expected" or "predicted" to have a meaningful impact on the overall abuse of the product.[35] Yet, without a single example to date of post-market studies confirming the predictive quality of the recommended premarketing studies, the validity of FDA's current approach to abuse-deterrent labeling remains hypothetical. Indeed, FDA acknowledges as much in its Guidance: "FDA has limited data correlating the abuse-deterrent properties of certain opioid drug products, as demonstrated by premarket studies, with the impact of those properties on abuse or adverse events associated with abuse in the post-approval setting."[36] Likewise, in the briefing document for MNK-812's advisory committee meeting, FDA states, "Public health benefits of abuse-deterrent opioid analgesics have been proposed, though no data demonstrating such benefit have been submitted and reviewed by FDA, and published studies evaluating such benefits have limitations."[37] To date eight years later, and despite FDA's decision to approve additional opioids with so-called abuse-deterrent properties, real-world data demonstrating the actual effectiveness of abuse-deterrent properties is non-existent. This point was made clear during a discussion between AADPAC chairman Raeford E. Brown, Jr., M.D., FAAP, and FDA epidemiologist Judy Staffa, Ph.D., R.Ph., at an advisory committee meeting for yet another flawed ADF product, RoxyBond (which would also ultimately be approved by FDA[38]). The following exchange between Dr. Brown and Dr. Staffa occurred during a discussion regarding the clinical relevance of HAP results and whether they can be extrapolated to forecast real-world rates of abuse:

> Dr. Brown: "Judy, can we use this data? Does it make sense for us to think of this as something that is useful for us to use against other products, or do we need to –"

[33] Consistent with this regulatory approval scheme, FDA requires abuse-deterrent labeling that lists all three of those categories of studies, thus further suggesting that these studies have greater significance than what sound science supports.
[34] See FDA, *Guidance for Industry: Abuse-Deterrent Opioids — Evaluation and Labeling*, at 5 (Apr. 2015) ("A-D Labeling Guidance" or "Guidance").
[35] See id. at 22.
[36] *Id.*
[37] See n. 24 at 59.
[38] PMRS, Petition for Stay of Action, Docket No. FDA-2017-P-3064 (May 11, 2017). Accessed on November 13, 2018 from https://www.regulations.gov/contentStreamer?documentId=FDA-2017-P-3064-0001&attachmentNumber=1&contentType=pdf

> Dr. Staffa: "In my opinion, no, because I think, again, this is just too crude. And remember, none of the nine products that were approved actually have, to FDA's satisfaction, postmarketing data that actually demonstrates that they have reduced abuse in the real world and that that reduction is due to the product."[39]

Further, FDA's recommendation that sponsors conduct HAP studies is particularly at odds with the statutory requirement that a product's purported abuse-deterrent properties be supported by substantial evidence. This is, in part, because HAP studies do not, and cannot, constitute adequate and well-controlled studies. HAP studies lack many of the characteristics of adequate and well-controlled studies that are set forth in FDA's regulations, including, among other things, "adequate measures . . . taken to minimize bias," "methods of assessment of subjects' response [that] are well-defined and reliable," and "an analysis of the results of the study adequate to assess the effects of the drug."[40,41]

The numerous HAP studies conducted to date for purportedly abuse-deterrent products cannot support a meaningful abuse-deterrent effect because such studies are subjective, not reproducible, and lack scientific foundation.[42] For example, pain experts have noted that the subjective responses of HAP study participants appear poorly correlated with objective (i.e., directly measurable) in vivo parameters. Dr. Edward Sellers, M.D., Ph.D., FRCPC, FACP, Professor Emeritus at University of Toronto, and a clinical pharmacologist who has performed over 100 abuse-potential studies, describes the scientific foundation of these studies at the September 11, 2015 Joint AADPAC/DSaRM advisory meeting, in testimony offered on behalf of the drug sponsor.

> "One important question that has to be answered is what are the data that inform the relationship of concentration and effect, both efficacy and safety….If you take

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[39] U.S. Food and Drug Administration, Center for Drug Evaluation and Research. *JOINT MEETING OF THE ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE (AADPAC) AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE (DSaRM)*, April 5, 2017. Transcript. Accessed November 13, 2018 from https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM564514.pdf

[40] PMRS has previously noted that HAP studies do not even appear to adhere to FDA's own recommendations in the A-D Labeling Guidance that such studies be "scientifically rigorous" and provide "data analyses to permit a meaningful statistical analysis." PMRS Citizen Petition, FDA Docket No. FDA-2016-P-0645-0001, at 5 (Feb. 19, 2016).

[41] See 21 C.F.R. § 314.126(b)(5)-(7).

[42] FDA's reliance on these flawed studies also has had a significant economic impact given decisions such as the granting of a three-year exclusivity period to reformulated OxyContin (based on single subjective OxyContin HAP study OTR1018 which fails to meet the required standard of adequate and well-controlled testing), as well as the removal of original OxyContin from the Orange Book for safety reasons. See additionally FDA Docket No. FDA-2016-P-0645.

> the concentrations at the time of Emax on the liking-at-the-moment scale, it will probably come as no surprise to you that there actually is a **very, very poor correlation**. The correlation—the R squared—is 0.09. …
>
> "If you go to the therapeutic chronic dosing situation that we are looking at here, again, you are **very hard-pressed to find any data** that allow you to predict in a given patient what you are going to get. Now, to me, because I've worked in the area for so long, this isn't all that surprising, because the sources of variation at the level of the brain and the receptor, intracellular transduction membranes and so forth, is really much, much larger than the variation you get with the kinetics. And that's because you have, of course, in the chronic dosing situation, prior administration of opiates, and, of course, you have a whole slew of genetic and epigenetic differences among individuals that basically take the population and make their sensitivity quite wide." (emphasis added)[43]

FDA's Guidance itself recognizes that "liking" studies are subjective and lack rigor ("evaluating the subjective effects of drugs").[44]

Both the FDA and institutional review boards should have prevented patients from participating in these trials. Patient exposure to these subjective and flawed studies is unethical.

In its February 2016 Petition, PMRS requested that FDA "[r]emove Category 3 human abuse-deterrent (liking) studies from the [AD Opioid Evaluation and Labeling] Guidance and as a requirement for approval of drug products with potentially abuse deterrent properties" because liking studies are "inherently flawed, subjective, and highly prone to manipulation."[45] PMRS reiterated this concern in a letter reply to FDA's interim response[46] and during the advisory committee meeting for VANTRELA ER.[47]

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[43] U.S. Food and Drug Administration, Center for Drug Evaluation and Research. *JOINT MEETING OF THE ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE (AADPAC) AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE (DSaRM)*, September 11, 2015. Transcript, pp. 174-175, Accessed November 13, 2018 from https://wayback.archive-it.org/7993/20170404144241/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM478974.pdf

[44] Guidance, p. 12.

[45] February 2016 Petition, at 3.

[46] Letter from Edwin R. Thompson, President, Pharmaceutical Manufacturing Research Services, Inc., to Carol J. Bennett, Deputy Director, Office of Regulatory Policy, CDER, Docket No. FDA-2016-P-0645, at 3 (Aug. 25, 2016).

[47] *See, e.g.*, Transcript, Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM), at 135 (Jun. 7, 2016), https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM516486.pdf (last accessed November 13, 2018) ("Liking studies are not valid scientific evidence and should not be a requirement for abuse-deterrent labeling, nor should they be used to approve abuse-deterrent labeling.").

The endpoints of MNK-812's abuse potential studies consist of the same pharmacodynamic "drug liking" assessments[48] which have repeatedly been demonstrated to be inherently flawed. The methodology used by FDA for approval of abuse-deterrent labeling for opioids is illegal, unscientific, misguided, and misleading.

2. FDA's Methodology Results in False and Misleading Labeling in Violation of the FD&C Act

Even assuming in arguendo that it is the statutory prohibition against "false and misleading" labeling that applies to abuse-deterrent labeling—and not the substantial evidence standard—FDA's current approach still fails. The FD&C Act prohibits labeling that "based on a fair evaluation of all material facts . . . is false or misleading in any particular."[49] CDER's current approach to abuse-deterrent labeling incorporates data and information from scientifically flawed and non-predictive premarket studies. As previously discussed, the validity of premarket studies in predicting abuse potential is purely hypothetical. Simply put, the premarket studies that FDA requires and relies upon to support its notion of abuse-deterrent labeling are scientifically suspect at best. Moreover, inclusion of this data and information has unintended negative consequences on public health by providing physicians with greater promise than merited that they can prescribe opioids safely so long as the product prescribed is labeled as abuse-deterrent.

Accordingly, and as discussed in detail below, FDA's prior approval of other opioids with purported claims of abuse deterrence is unlawful and scientifically unsound. The increased emphasis on so-called abuse-deterrent formulations and labeling in response to the opioid epidemic has resulted in the market entry of additional misbranded products that pose a significant public health risk. Such false and misleading labeling serves only to confuse prescribers and patients about what the product is and, more importantly, is not. Moreover, despite the approval of these products, the opioid epidemic continues to escalate, and the number of overdoses and deaths continue to increase.

As an example, the FDA approved abuse-deterrent labeling for reformulated OxyContin for the intravenous route stating, "When subjected to an aqueous environment, OXYCONTIN gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle."

However, the FDA's conclusions of syringability must be incorrect, as the patent itself under which the drug was formulated requires passage through a needle. For example, claim 1 of US

[48] *See* n.24 at §6.
[49] 21 U.S.C. § 355(d)(7)

Pat. No. 7,776,314 provides:[50]: "A parenteral abuse-proofed solid dosage form for oral administration… such that an aqueous extract obtained from the dosage form with 10 ml of water at 25° C. forms a gel **which can still pass through a needle having a diameter of 0.9 mm** and remains visually distinguishable when introduced by a needle into a further quantity of an aqueous liquid." (emphasis added)[51]

Moreover, the scientific findings by FDA CSS contradict the conclusions of Dr. Bob A. Rappaport (then-Division Director) and Dr. Douglas C. Throckmorten (Deputy Director CDER). The CSS evaluation of OxyContin's intravenous abuse-deterrent properties reported, "Water is also effective in extracting oxycodone HCl from intact tablets of reformulated OxyContin. Thus, **a simple water extraction procedure can afford clinically significant amounts of oxycodone from high strengths of intact and crushed tablets of both the original and reformulated product**." (emphasis added)[52] In contrast, in his recommendation to approve abuse-deterrent labeling for OxyContin, Dr. Rappaport stated, "These features also render the product **almost impossible to dissolve, syringe and inject**." (emphasis added)[53] Similarly, in his recommendation to approve OxyContin's abuse-deterrent labeling, Dr. Throckmorten concluded, "The in vitro testing was sufficient to demonstrate that **OCR prevents oxycodone from being drawn into a syringe** to any meaningful extent." (emphasis added)[54] The recommendations of Dr. Rappaport and Dr. Throckmorten—which appear to contradict the findings of CSS—are reflected in the abuse-deterrent labeling approved for OxyContin: "When subjected to an aqueous environment, OxyContin gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle." Because reformulated OxyContin can be readily prepared for injection—despite claims by certain FDA officials to the contrary—the product's labeling contains claims that are false and misleading and, thus, the product is misbranded.

Indeed, in a February 2016 Citizen Petition (FDA-2016-P-0645), PMRS presented evidence—including a film demonstrating the ease with which reformulated OxyContin can be extracted

[50] U.S. Food and Drug Administration, Orange Book. Patent and Exclusivity for: N022272. Accessed November 13, 2018 from https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=022272&Appl_type=N

[51] United States Patent No. US 7,776,314 B2, Bartholomäus et al, August 17, 2010. Accessed November 13, 2018 from https://patentimages.storage.googleapis.com/f4/ff/a8/814e4311dd45e0/US7776314.pdf

[52] U.S. Food and Drug Administration, Center for Drug Evaluation and Research. OxyContin NDA 22-272, S-014 *Other Reviews, Memorandum*, April 11, 2013, p. 272. Accessed November 13, 2018 from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/022272Orig1s014OtherR.pdf

[53] U.S. Food and Drug Administration, Center for Drug Evaluation and Research. OxyContin NDA 22-272, S-014 *Division Director Review, Addendum, April 16, 2013*, p. 2, accessed November 13, 2018 from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/022272Orig1s014SumR.pdf

[54] U.S. Food and Drug Administration, Center for Drug Evaluation and Research. OxyContin NDA 22-272, S-014 *Office Director Memo*, April 16, 2013, p. 9, accessed November 13, 2018 from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/022272Orig1s014ODMemo.pdf

from intact tablets—documenting that reformulated OxyContin lacks abuse-deterrent intranasal[55] and intravenous properties. Thus, "exceedingly easy" methods of extracting active ingredients to high purity from FDA-approved so-called "abuse-deterrent" formulations have been known for years and can be performed by unskilled individuals with ease.[56,57]

Nonetheless, over two and a half years later, the FDA has been unable to refute this evidence and unwilling to publicly explain its actions. By not responding, FDA's inaction has allowed OxyContin to continue to be marketed with abuse-deterrent labeling that is false and misleading.

3. CDER's Imposition of Approval Requirement Based on Guidance Exceeds the Legal Authority Accorded to an Agency

Not only does its current approach to abuse-deterrent labeling fail to meet the requisite statutory standard, CDER treats it as binding in clear violation of the Administrative Procedure Act (APA).[58]

Under the APA, a court shall "hold unlawful and set aside" any agency action that was promulgated "without observance of procedure required by law."[59] As one example, CDER's treatment of its A-D Labeling Guidance as binding equates to a "substantive" or "legislative" rule that should have been enacted through the notice-and-comment rulemaking procedure.[60] A rule is legislative, rather than interpretive, when "in the absence of the rule there would not be an adequate legislative basis for ... agency action to confer benefits or ensure the performance of duties . . ."[61]

The U.S. Department of Justice reiterated this well-established principle of administrative law earlier this year, cautioning that guidance documents "do not have the binding force or effect of law and should not be used as a substitute for rulemaking."[62]

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[55] More discussion in regards to OxyContin intranasal abuse will be discussed in Section V.4.(B) *infra*.
[56] FDA Docket No. FDA-2016-P-0645, February 26, 2016. Accessed November 13, 2018 from: https://www.regulations.gov/docket?D=FDA-2016-P-0645
[57] "OxyContin Modification" https://www.regulations.gov/document?D=FDA-2018-N-0188-0273
[58] *See* n. 25 at https://www.regulations.gov/contentStreamer?documentId=FDA-2018-N-0188-0277&attachmentNumber=1&contentType=pdf
[59] 5 U.S.C. § 706(2)(D)
[60] 5 U.S.C. § 553
[61] Nat'l Pharm. Alliance v. Henney, 47 F. Supp. 2d 37, 41 (D.D.C. 1999).
[62] DOJ, Memorandum for Heads of Civil Litigating Components, United States Attorneys: Limiting Use of Agency Guidance Documents In Affirmative Civil Enforcement Cases," from Associate Attorney General Rachel Brand, November 13, 2018 https://www.justice.gov/file/1028756/download

FDA's own regulations governing the agency's administrative practice and procedures recognize the non-binding nature of agency guidance. Pursuant to FDA's Good Guidance Practices regulation, "Guidance documents do not establish legally enforceable rights or responsibilities" or operate to "legally bind the public."[63] In line with this admonition as to an agency's use of a guidance in lieu of APA rulemaking, PMRS further notes that each and every final guidance document issued by FDA, including the very A-D Labeling Guidance at issue here, bears a prominent black box caution in bolded print:

> This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.[64]

In addition, FDA guidance documents, including the one at issue here, include the following header: "*Contains Non-binding Recommendations*". The A-D Labeling Guidance further includes the following text on the very first page:

> This guidance explains FDA's current thinking about the studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties. The guidance *makes recommendations* about how those studies should be performed and evaluated and discusses how to describe those studies and their implications in product labeling.
> . . .
> In general, FDA's guidance documents *do not establish legally enforceable responsibilities*. Instead, guidances describe the Agency's current thinking on a topic and s*hould be viewed only as recommendations*, unless specific regulatory or statutory requirements are cited. *The use of the word should in Agency guidances means that something is suggested or recommended, but not required*. [65]

The importance of the agency transparency and accountability aspect of notice-and-comment rulemaking that is absent from the guidance process cannot be overestimated. FDA's regulation governing the rulemaking process is detailed and requires FDA to follow a rigorous process. It provides, for example, that the final regulation will have a preamble that includes, among other things, "a summary of each type of comment submitted on the proposal and the Commissioner's

[63] 21 C.F.R. § 10.115
[64] FDA includes a similar black boxed statement in all of its draft guidance documents, though with a slightly modified preface to account for the draft status.
[65] A-D Labeling Guidance, at 1 (emphasis added).

conclusions with respect to each" and "a thorough and comprehensible explanation of the reasons for the Commissioner's decision on each issue."[66]

The FDA has arbitrarily and capriciously approved opioid abuse-deterrent labeling using FDA guidance to supersede the FD&C Act. The FDA effectively converted a nonbinding guidance document into a requirement for abuse-deterrent labeling that has the force and effect of the law. At the same time, the FDA has failed to establish a standard under the FD&C Act. The result is the misbranding of opioids, providing physicians and patients with a false sense of security, leading to the overprescribing of opioids. The FDA should take a lawful approach rather than this one set forth in a Guidance document[67,68].

4. FDA's Disparate Treatment of Abuse-Deterrent Labeling For Previously-Approved Products Demonstrates it is Unlawful, Lacks Scientific Merit, and Further Endangers Public Health.

A. The FDA Does Not Utilize a Legal Standard for Approving Abuse-Deterrent Labeling for Opioid Products

The APA requires a reviewing court to "hold unlawful and set aside agency action, findings, and conclusions found to be . . . arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law..."[69] Under the FD&C Act, the "disparate treatment of functionally indistinguishable products is the essence of the meaning of arbitrary and capricious."[70] Where an agency applies "different standards to similarly situated entities and fails to support this disparate treatment with a reasoned explanation and substantial evidence in the record, its action is arbitrary and capricious and cannot be upheld."[71]

The FDA has applied multiple standards for evaluating the abuse-deterrent properties of opioid products which has resulted in unpredictable and logically inconsistent decisions even when evaluating drug products with virtually identical abuse-deterrent properties. This ad hoc approach to approving abuse-deterrent opioids is arbitrary, capricious, and an abuse of the Agency's discretion. The following examples highlight FDA's failure to adhere to a consistent approach when evaluating opioids formulated with abuse-deterrent properties.

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[66] 21 C.F.R. § 10.40(c)(3)(vii).
[67] *See* n.62.
[68] U.S. Department of Justice, Federal Bar Association Qui Tam Conference, accessed November 13, 2018 from https://www.justice.gov/opa/speech/deputy-associate-attorney-general-stephen-cox-delivers-remarks-federal-bar-association
[69] 5 U.S.C. § 706(2)(A).
[70] Bracco Diagnostics, Inc. v. Shalala, 963 F.Supp. 20, 28 (D.D.C. 1997).
[71] Burlington N. & Santa Fe Ry. Co. v. Surface Transp. Bd., 403 F.3d 771, 777 (D.C. Cir. 2005).

First, although FDA approved reformulated Opana ER (NDA 21-610) in December 2011, the Agency concluded that the data submitted did not support abuse-deterrent labeling for intranasal and intravenous routes of abuse. In May 2013, FDA again denied abuse-deterrent labeling for reformulated Opana ER when it issued a complete response letter to a supplemental NDA (sNDA) that was submitted in February 2013, even though that submission was bolstered by preliminary post-marketing epidemiology data on Opana ER. In stark contrast, in April 2013, FDA approved abuse-deterrent labeling for reformulated OxyContin (NDA 22-272/S-014) with claims related to crushing, breaking, intranasal, and intravenous abuse. This decision was remarkable because reformulated Opana ER and reformulated OxyContin share virtually identical abuse-deterrent properties. For example, in evaluating the comparative abuse-deterrent properties of reformulated Opana ER, the FDA reported that Opana ER's resistance to crushing and grinding (i.e., particle size reduction) is comparable to that of OxyContin ADF. FDA also reported that the performance of reformulated Opana ER in the small volume extraction (SVE) studies demonstrated that the product is "comparable" to reformulated OxyContin and, in some experiments, even superior.

Second, the contradictory outcomes resulting from FDA's evaluation of the abuse-deterrent properties of reformulated Opana ER and reformulated OxyContin —despite the fact these two products share virtually identical abuse-deterrent properties and their applications were under review at the same time—is further highlighted by examining the conclusions of FDA's Controlled Substance Staff (CSS). When reviewing reformulated Opana ER, FDA CSS concluded, "OPR's extended-release features can be compromised, causing the product to "dose dump," when subjected to other forms of manipulation such as cutting, grinding, or chewing."[72] FDA presumably took CSS's conclusions into consideration when deciding not to approve abuse-deterrent labeling for reformulated Opana ER.

Similarly, when reviewing reformulated OxyContin, FDA CSS concluded, "Upon chewing vigorously, ORF and OC products are bioequivalent with respect to oxycodone Cmax and area under the curve. Reformulated OxyContin has no meaningful advantage in breaking and crushing over original OxyContin."[73] Nonetheless, and in stark contrast to the Agency's decision on reformulated Opana ER, FDA proceeded to approve abuse-deterrent labeling for reformulated OxyContin which included the following claim: "relative to original OXYCONTIN, there is an increase in the ability of OXYCONTIN to resist crushing, breaking,

[72] FDA Docket No. FDA 2012-P-0895, May 10 2013, p. 5, accessed November 13, 2018 from https://www.regulations.gov/contentStreamer?documentId=FDA-2012-P-0895-0014&attachmentNumber=1&contentType=pdf

[73] U.S. Food and Drug Administration, Center for Drug Evaluation and Research. OxyContin NDA 22-272, S-014 Division Director Review, February 6, 2013, p. 8, accessed November 13, 2018 from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/022272Orig1s014SumR.pdf

and dissolution using a variety of tools and solvents."[74] This disparate result seemingly ignores the conclusions of FDA CSS and directly conflicts with the Agency's decision to deny abuse-deterrent labeling to reformulated Opana ER.

In addition, FDA CSS re-evaluated reformulated Opana ER's abuse-deterrent properties by the intranasal route in 2017 and—pivotal to its recommendation to remove reformulated Opana ER from the market—concluded that the previously-submitted studies "support a deterrent effect of reformulated OPANA ER to abuse by intranasal administration."[75] This conclusion directly conflicts with FDA's previous decisions in 2011 and 2013 to deny abuse-deterrent labeling for the intranasal route to reformulated Opana ER.

FDA's decision to approve reformulated OxyContin with abuse-deterrent labeling for the intranasal route is also contradictory. The FDA-approved labeling for reformulated OxyContin states, "The data from the clinical study, along with support from the in vitro data, also indicate that OXYCONTIN has physicochemical properties that are expected to reduce abuse via the intranasal route."[76] However, in a February 2016 Citizen Petition (FDA-2016-P-0645), PMRS presented FDA with evidence that reformulated OxyContin does not in fact possess abuse-deterrent properties for the intranasal route of administration. Such evidence includes FDA's statement that reformulated OxyContin "can still be crushed to a fine powder using a coffee grinder", reliance on inadequate and not well-controlled liking study OTR 1018 ("OTR 1018 was essential to approval" and "no other data exists to support approval of this supplement"), and the lack of any statistically meaningful abuse deterrent effect.

Last, FDA CSS evaluated both reformulated Opana ER and reformulated OxyContin for abuse by the intravenous route and reached opposite conclusions when deciding whether to approve abuse-deterrent labeling for the intravenous route. This, again, is remarkable as both drug products share virtually identical physicochemical properties. In fact, both drug products are licensed by the same company, are protected under the same patents, and have virtually the same excipients. Thus, if tested under the same conditions, both drug products are expected to produce virtually identical results. Indeed, as previously discussed, FDA CSS evaluated reformulated Opana ER using small volume extraction and reported comparable results to

[74] U.S. Food and Drug Administration, *Highlights of Prescribing Information OxyContin*, April 2013, p. 19, accessed November 13, 2018 from http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf

[75] U.S. Food and Drug Administration, FDA Presentations for the March 13-14, 2017 Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee, "Intranasal Studies for Opana ER and Integration of In Vitro Findings", p. 12, accessed November 13, 2018 from https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM547235.pdf

[76] *See* n. 74 at p. 21.

OxyContin ADF. And, when tested under the same conditions, both drug products can be made to gel and both drug products can equally be manipulated to circumvent gelling. For example, in its evaluation of reformulated OxyContin, FDA CSS reported, "Water is also effective in extracting oxycodone HCl from intact tablets of reformulated OxyContin. Thus, a simple water extraction procedure can afford clinically significant amounts of oxycodone from high strengths of intact and crushed tablets of both the original and reformulated product."[77] This finding suggests that both products can easily be extracted and injected by unskilled and uneducated abusers to virtually equal label claim and purity. Nonetheless, FDA approved abuse-deterrent labeling for reformulated OxyContin with the following claim pertaining to intravenous abuse: "When subjected to an aqueous environment, OXYCONTIN gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle."[78] In light of the evidence refuting this claim, reformulated OxyContin is misbranded, and FDA should revoke, among other things, its intravenous abuse-deterrent labeling. Moreover, given that the products share similar physicochemical properties, FDA's decision to approve abuse-deterrent labeling for the intravenous route for reformulated OxyContin, while denying this labeling to reformulated Opana ER, is arbitrary, capricious, and an abuse of the Agency's discretion. As the evidence presented clearly indicates, neither reformulated OxyContin nor reformulated Opana ER should have been granted intravenous abuse-deterrent labeling.

B. **FDA's Utilization of Abuse-Deterrent Postmarketing Data Is Unscientific**

In their review of MNK-812, FDA, as well as members of AADPAC and DSaRM, have made reference to risks associated with ADF drug formulations, largely stemming from concerns relating to Opana ER. FDA in particular has indicated that sponsors are now required to provide a safety assessment of the potential effects and risks associated with abuse of the final drug product.[79] This is a significant change from the previous agency position in which FDA DAAAP informed the public in a July 2017 Advisory Committee meeting that, "The Agency does not require that oral drug product excipients be assessed for safety for intravenous or other unintended routes."[80] FDA's rationale for these changes is misguided and misinformed. FDA's

[77] *See* n. 52 at p. 4.
[78] See n. 74.
[79] James M. Tolliver, PhD. *Comments Regarding Category 3 Oral Study and Category 1 Smoking Study*, June 26, 2018, p. 56. Accessed November 13, 2018 from https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM612437.pdf
[80] James M. Tolliver, PhD. Need for Human Abuse Potential Studies for Evaluation of NDA 209-653, June 26, 2017, p. 29. Accessed November 13, 2018 from https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM569141.pdf

analysis of postmarketing data on Opana ER which led to the request to withdraw the product is incorrect.

The facts which led FDA to assume a reduction in intranasal abuse in Opana ER are as follows:

1. Opana ER and OxyContin formulations are nearly identical and both contain a minimum of 60% high molecular weight PEO.

Table 1 — Opana ER and OxyContin formulations

Opana ER[81]	**OxyContin**[82]
high molecular weight polyethylene oxide	high molecular weight polyethylene oxide
hypromellose	hypromellose
polyethylene glycol (Macrogol)	polyethylene glycol 400
α tocopherol	magnesium stearate
citric acid	butylated hydroxytoluene (BHT)
Total Weight: 215mg (any strength Opana ER)	Total Weight: 265mg (OxyContin 80mg strength)

2. Opana ER and OxyContin required cutting forces are below chewing breaking strengths:[83]

Table 2 — Razor Blade Cutting Force

Sample	Opana ER 5mg	Opana ER 40mg	OxyContin 10mg	OxyContin 40mg	OxyContin 60mg	OxyContin 80mg
AVG Force (N)	127	131	45	43	46	48

Table 3 — Fracture Wedge Cutting Force

Sample	Opana ER 5mg	Opana ER 40mg	OxyContin 10mg	OxyContin 40mg	OxyContin 60mg	OxyContin 80mg
AVG Force (N)	156	141	149	93	104	95

[81] U.S. Food and Drug Administration, Center for Drug Evaluation and Research. *FDA Briefing Document - Joint Meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) Meeting*, March 13-14, 2017, p. 101. Accessed November 13, 2018 from https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM545760.pdf

[82] U.S. Food and Drug Administration, OxyContin NDA 20553, S-060, OxyContin Package insert, September 2, 2009.

[83] PMRS, Inc., AS03636.00 - *Data Summary Report of a Cutting Force Method for Multiple Formulations of CII Narcotic Drug Products.* April 10, 2014.

3. In 2013 reformulated Opana ER (OPR), generic oxymorphone ER, and reformulated OxyContin (OCR) are commercially available to the marketplace.
4. The data show a rising prevalence of nasal OP abuse during the pre-period (15-month period from reformulated OxyContin introduction and prior to introduction of reformulated Opana ER)[84]
5. Post-period (3-year period following the market transition period of Opana ER reformulation and generic oxymorphone introduction[85]) OPR abuse (IN) prevalence returned to levels not significantly different from OP abuse prevalence in the earlier 6-quarter pre-period prior to OxyContin's introduction.[86]
6. "During the post-period, the prevalence of OPR abuse via snorting remained relatively stable at levels lower than those just prior to Opana ER's reformulation but similar to those seen early in the pre-period, and the prevalence of generic oxymorphone ER snorting during the post-period was consistently higher than that for OPR."[87]
7. "Using the tablets-dispensed denominator generic oxymorphone ER demonstrated the highest nasal abuse rates of all the studied opioids. During the post-period, tablet-adjusted nasal abuse rates for OPR were lower than for generic oxymorphone ER and more similar to oxymorphone IR and oxycodone ER."[88]
8. "The mean Opana ER injection abuse prevalence increased markedly across the three study periods," from 0.05 to 0.21 abuse reports per 100 assessments in the first and second pre-periods, respectively, then to 0.81 per 100 assessments in the post-period.[89] "However, the mean injection abuse prevalence for generic oxymorphone ER was not significantly different from that for OPR in the post-period."[90]
9. "In total, 59 cases of TMA associated with intravenous abuse of Opana ER have been identified in FAERS from December 9, 2011 through June 1, 2016."[91] There were a total of 74 cases—including the 59 TMA events—reported for intravenous abuse for Opana ER from 2012 through 2016 (31 cases in 2012, 30 cases in 2013, 8 cases in 2014, 3 cases in 2015 and 2 cases in 2016).[92]

[84] *See* n. 81 at p. 170.
[85] *See* n. 81 at p. 212.
[86] *Id* at p. 229.
[87] *Id* at p. 230.
[88] *Id* at p. 231.
[89] *Id* at p. 233.
[90] *Id* at p. 232.
[91] *Id* at p. 164.
[92] *Id* at p. 164.

10. DPV search for TMA cases associated with other opioids formulated with a PEO matrix intended to resist crushing and dissolving in solution identified three foreign cases.[93]

The FDA's decision was to recommend removal of reformulated Opana ER (OPR) from the market because abuse of OPR shifted from IN to IV, with the addition of incremental harms from TTP and HIV, claiming the root cause was the product's reformulation.[94]

However, the dataset relied on by FDA also clearly shows the following facts:

- There was an increase in Opana ER intranasal abuse after the introduction of reformulated OxyContin (AUG 2010) and prior to the introduction of reformulated Opana ER.[95]
- Although there was a decrease in Opana ER intranasal abuse after the introduction of Opana ER reformulation, the level merely returned to the pre-reformulated OxyContin level.[96]
- There was a significant addition of generic oxymorphone ER intranasal abuse upon its introduction to the market, months after the introduction of reformulated Opana ER. The sum of reformulated Opana ER and generic oxymorphone ER produced an increase in intranasal abuse greater than prior to OPR introduction.[97]
- Oxymorphone ER intranasal abuse continued to grow after the introduction of OCR and OPR.
- Intranasal Abuse Conclusion: The apparent decline in reformulated Opana ER intranasal abuse instead was a migration to generic oxymorphone intranasal abuse. OP intranasal abuse increased with the introduction of OCR. With the introduction of OPR, Opana ER returned to the pre-introduction OCR level. Generic oxymorphone ER introduction continued the growth of oxymorphone intranasal abuse. Oxymorphone ER intranasal abuse continued to grow after the combined introduction of OPR and generic oxymorphone ER.

The FDA concluded that the reduction in intranasal abuse after the introduction of reformulated Opana ER caused an increase in IV abuse of reformulated Opana ER. Per FDA, patients switched from IN to IV.

[93] *Id* at pp. 164-165.
[94] U.S. Food and Drug Administration, *FDA News Release - FDA requests removal of Opana ER for risks related to abuse*, June 8, 2017. Accessed November 13, 2018 from https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm562401.htm
[95] *See* n. 81 at pp. 231-232.
[96] *Id* at p. 229.
[97] *Id* at p. 230.

The facts in regard to intravenous abuse are as follows:

- Opana ER IV abuse increased starting in 2009 and continued to increase during the introduction of OCR, the introduction of OPR and generic oxymorphone ER.
- Reformulated Opana ER increased significantly in IV abuse after market entry accompanied with a similar addition of IV abuse by the entry of generic oxymorphone and increases by oxymorphone IR and morphine ER products. "Both the prevalence per 100 assessments and the abuse rate per 10,000 tablets dispensed were significantly greater for generic oxymorphone ER than for OPR during the post-period."[98]

Intravenous Abuse Conclusion: Oxymorphone ER IV abuse started to increase in 2009 and continued to increase through the introduction of OCR, OPR and generic oxymorphone ER. Both oxymorphone ER IN and IV abuse have been growing since the introduction of OCR. Rates for IV abuse per 10,000 tablets dispensed for all opioids have increased or are steady through 2016, even for purportedly abuse-deterrent formulations such as OxyContin.[99] ADF IV properties have failed to reduce IV abuse.

As can be seen in Figure 3 provided by FDA (emphasis added), the per-10,000 tablet rate of IV abuse for both reformulated Opana ER and generic oxymorphone ER are correlated. As generic oxymorphone ER is an equivalent formulation to original Opana ER, it is incorrect to suggest that the formulation of reformulated Opana ER in any way lead to increased intravenous

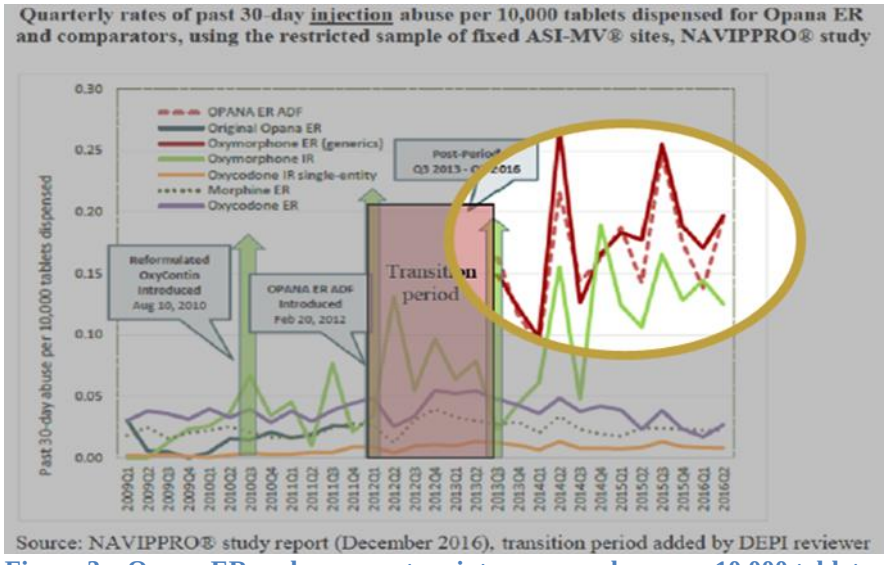

Figure 3 – Opana ER and comparators intravenous abuse per 10,000 tablets (emphasis added)

[98] *See* n. 81 at p. 169.
[99] *Id* at p. 172.

abuse. Intravenous abuse of either original Opana ER, the functionally equivalent generic oxymorphone ER, or reformulated Opana ER can be performed with comparable ease.

At the RADARS annual meeting in 2017, FDA epidemiologist Staffa conceded many of the same conclusions posited above, in contradiction to the narrative promoted by FDA at the both the Opana ER advisory committee meeting and in the FDA press release for the Opana ER withdrawal request:

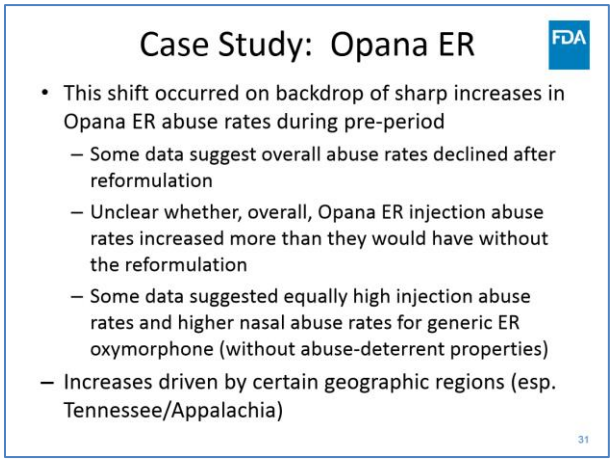

Figure 4 – Opana ER epidemiology[100]

Furthermore, the flawed abuse analyses lead to erroneous conclusions in regard to the consequences. The facts on the reported cases of TMA/TTP are as follows:

- In 2012, 15 cases of TTP-like illness were identified in Tennessee (none were fatal), including 14 who had reported injecting reformulated Opana ER.[101] The 14 cases were reported from July to October 2012. 12 cases were from the same or nearby counties.[102]
- FAERS search produced 29 cases of intravenous abuse of Opana ER and TMA from December 9, 2011 through March 26, 2013. Most were from a single rural county in

[100] Judy A. Staffa, PhD, RPh, *Evaluating the Impact of Abuse Deterrent Formulations: Methodological Challenges in Postmarketing Data*, May 12, 2017, p. 31. Accessed November 13, 2018 from https://www.radars.org/system/events/RADARS%20System%202017%20Annual%20Meeting_Staffa.pdf.tmp
[101] *See* n. 81 at p.183.
[102] Centers for Disease Control and Prevention. *Thrombotic Thrombocytopenic Purpura (TTP)–Like Illness Associated with Intravenous Opana ER Abuse — Tennessee, 2012*, Morbidity and Mortality Weekly Report, January 11, 2013. Accessed November 13, 2018 from https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6201a1.htm?s_cid=mm6201a1_w

Tennessee. Thirty additional cases were identified from March 27, 2013 through June 1, 2016.[103]

- FAERS report of all reformulated Opana ER IV abuse listed 8 reports in 2014, 3 reports in 2015 and 2 reports in 2016.[104]
- "There was one FAERS case (#9498513) with an outcome of death. This death, reported in 2013, was due to intractable sepsis and endocarditis; the case further detailed that TTP improved considerably after three plasmapheresis treatments with recovery of platelet counts prior to death."[105]

The correct conclusion is that reformulated Opana ER-related TMA was localized, limited and corrected in a short period of time. Opioid abusers adapted and learned how to extract the API from PEO-containing opioid products (note that both reformulated OxyContin and Opana ER contain a minimum of 60% HMW PEO) and have learned how to extract oxymorphone from Opana ER without including excipients that cause TMA.

Finally, the facts and timeline on HIV:

- In January 2015 the Indiana State Department of Health (ISDH) reported an outbreak of HIV infection in a rural county in southeastern Indiana, and when updated in April 2015 involved 135 patients.
- 108 patients reported injection drug use and all reported dissolving and injecting tablets of oxymorphone as their drug of choice. Some patients reported injecting other drugs.
- At the March 13, 2017 advisory committee meeting, presentations by then-Indiana State Health Commissioner (and current U.S. Surgeon General) Jerome Adams, M.D., M.P.H., and CDC Senior Medical Advisor John T. Brooks, M.D. attributed the outbreak of HIV to needling-sharing associated with abuse of Opana ER.
- However, subsequent to the advisory committee meeting, the CDC write-up documented that injection drug use in this community "include crushing and cooking extended-release oxymorphone, most frequently 40mg tablets **not designed to resist crushing or dissolving.**" (emphasis added)[106]

This isolated outbreak of HIV cannot be attributed both to reformulated Opana ER as well as to oxymorphone tablets "not designed to resist crushing or dissolving". These two facts are incompatible. The conclusion should have been that the outbreak was associated with generic

[103] *See* n. 81 at p. 198.
[104] *Id* at p. 196.
[105] *Id* at p. 200.
[106] Centers for Disease Control and Prevention. *Community Outbreak of HIV Infection Linked to Injection Drug Use of Oxymorphone — Indiana, 2015*, Morbidity and Mortality Weekly Report, May 1, 2015. Accessed November 13, 2018 from https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6416a4.htm

oxymorphone ER and causal relationships and conclusions should have been directed to generic oxymorphone ER. Furthermore, even if additional evidence did implicate reformulated Opana ER as a factor in the outbreak, HIV transmission—an infection—clearly cannot be a function of a particular drug formulation. As described above, intravenous abuse rates for both reformulated Opana ER and generic oxymorphone ER are correlated, with rates for generic oxymorphone IR also close behind. Rates of intravenous use of all forms of oxymorphone were increasing prior to the Opana ER reformulation. To stop the spread of HIV due to intravenous abuse of oxymorphone, all oxymorphone products should have been removed from the market for reasons of safety, not just Opana ER.

FDA's extreme action—requesting a sponsor's withdrawal of a drug for reasons of safety—was taken in an absence of clear, actionable data, against the "signal" of treated 59 cases of TMA/TTP over a 5 ½ year period and a single fatality, against the backdrop of hundreds of millions of tablets[107] dispensed over the same period.

Furthermore, in remarks made at the Interagency Pain Research Coordinating Committee meeting in October 2017, DAAAP Division Director Sharon Hertz, M.D. stated:

> Within the agency, our deliberations very much try to include why these medications should not simply all be taken off the market. Sure, we can nip this whole thing in the bud—no more opioids. But what is that outcome? That's not an acceptable outcome. And that's why even when we were thinking about the risks associated with extended-release oxymorphone; it was a product-specific risk, not a drug substance risk. So we're trying to make sure that our actions—to the extent that they are interpreted the way they are intended—are so that access is preserved.[108]

Hertz gets the key conclusion completely wrong. The key driver of the increasing abuse of oxymorphone products is undoubtedly a drug substance risk, due to oxymorphone's comparably low (10%) bioavailability[109] compared to intranasal and intravenous routes. Even if FDA does not understand this fact, the abuse community certainly does.[110]

With evidence that overall, intranasal and intravenous abuse significantly increased with the introduction of generic oxymorphone, the FDA should have reached the opposite conclusion.

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[107] U.S. Department of Justice, Drug Enforcement Administration, Diversion Control Division. *AGGREGATE PRODUCTION QUOTA HISTORY FOR SELECTED SUBSTANCES*, November 15, 2017. Accessed November 13 2018 from https://www.deadiversion.usdoj.gov/quotas/quota_history.pdf

[108] *Interagency Pain Research Coordinating Committee - October 2017*. Video, 02:12:15. Accessed November 13, 2018 from https://videocast.nih.gov/summary.asp?Live=26523&bhcp=1

[109] *See* n. 75 at p.4.

[110] *Bioavailability/Half-life MEGA Thread*. Bluelight, August 18, 2006. Accessed November 13, 2018 from http://www.bluelight.org/vb/threads/266339-Bioavailability-Half-life-MEGA-Thread

Oxymorphone ER is a significant drug substance abuse risk, independent of reformulated Opana ER, and should be removed from the market.

C. **FDA's Route-Specific Abuse-Deterrent Labeling is Misleading**

Contrasting oxymorphone's oral bioavailability (10%) to oxycodone (60%-87%), it can be seen that the drug substance itself remains key to understanding the manner in which these drugs are predominantly abused. Based on the bioavailability, abuse of oxymorphone is directed to intravenous, and oxycodone to oral.

For oxycodone products, declaration of abuse deterrence for the nasal route is a mere smokescreen that does nothing to protect the American public. Despite FDA advocacy for the development and classification of products with claimed abuse-deterrent properties for this route, there is no scientific evidence that intranasal abuse of oxycodone is a more effective route of abuse for oxycodone than oral abuse. Furthermore, existing pharmacokinetic data actually refutes the nasal route of abuse as a means of providing a stronger or faster drug "high".

Multiple drug product sponsors have presented measurable, reproducible data to the FDA on oxycodone blood levels (Cmax and Tmax) for the oral and nasal routes of administration for 30 and 40 mg dosage strengths. This data includes both intact and manipulated dosage forms, as well as pure oxycodone (API) powder. This data has been aggregated in Figure 5 for Cmax, and Figure 6 for Tmax. In the context of abuse, a product with a higher Cmax (greater maximum blood concentration) and a lower Tmax (faster time to maximum concentration) is more prone to abuse. When evaluating Cmax between the nasal and oral routes of abuse, it is readily apparent the oral route offers an equal or greater Cmax when compared to nasal abuse. Similarly, when examining the Tmax for each route, it is also clear that the oral route offers an equal or faster high than the nasal route. These charts demonstrate that manipulated oxycodone taken orally is superior to manipulated oxycodone taken nasally (for both Cmax and Tmax). This data mandates several conclusions.

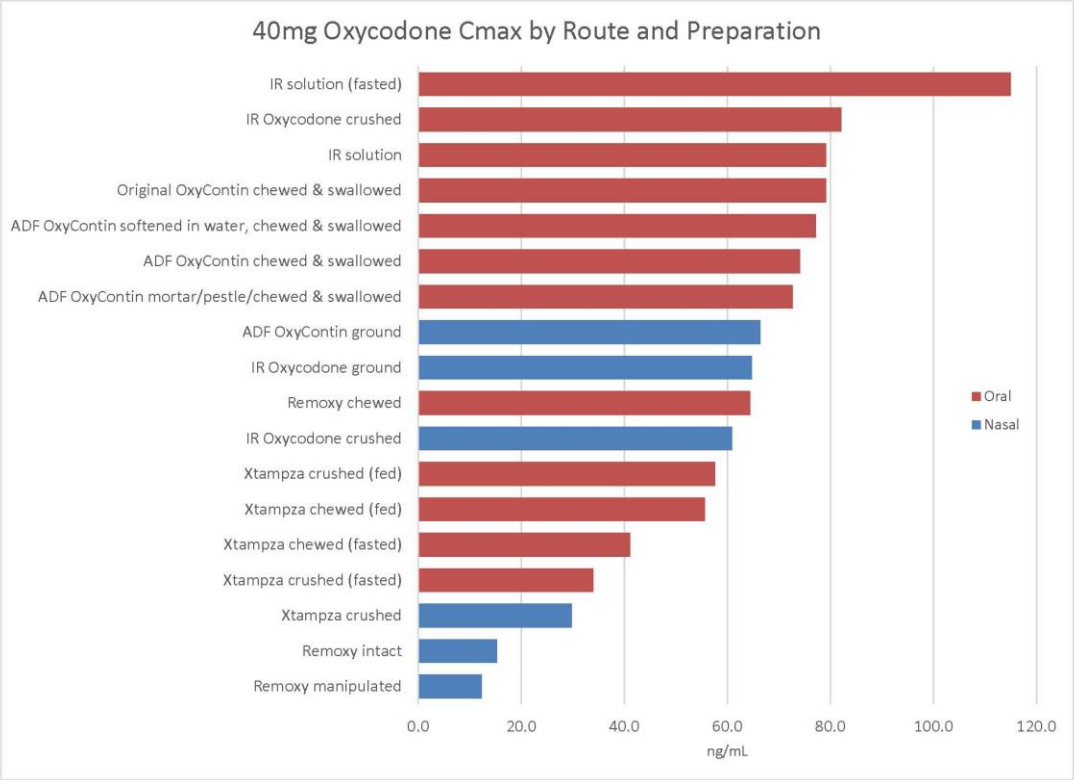

Figure 5 - 40mg Oxycodone Cmax by Route and Preparation

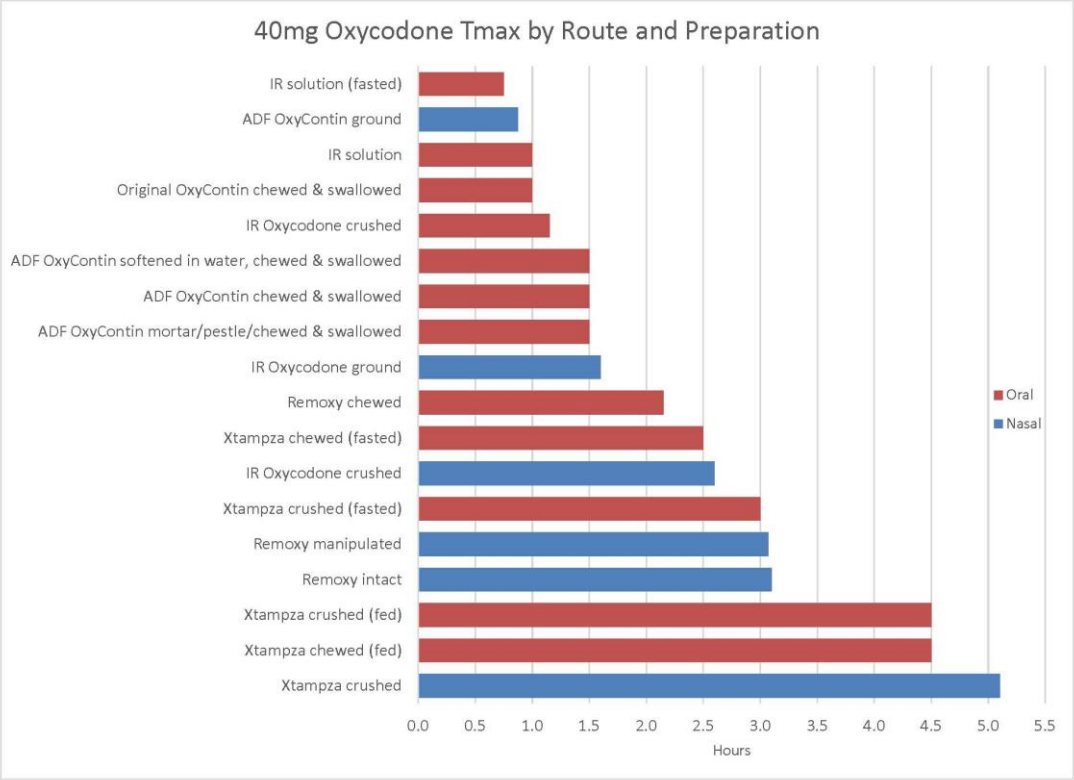

Figure 6 - 40mg Oxycodone Tmax by Route and Preparation

For oxycodone, oral is clearly the superior route of abuse when compared to nasal. Oral offers a greater high than intranasal administration, and this also comes at a faster rate. Additionally, this supports the conclusion that the oral route is a more dangerous route than the nasal route. Due to the greater and faster high, oral presents a greater potential for lethal overdose than intranasal administration. This is additionally supported by DEA medical examiner reports (data as of 2002[111]; referenced by FDA in 2013) which indicate that 96% of OxyContin deaths are due to oral abuse, compared to 2% for intravenous and 0.2% for intranasal.[112] Lastly, the nasal route is irrelevant to abuse deterrence in the context of oxycodone. Given the oral route's superior Cmax and Tmax, there is no incentive beyond preconceived and erroneous notions about the drug to abuse oxycodone intranasally.

[111] U.S Department of Justice, Drug Enforcement Administration, Office of Diversion Control. *Summary of Medical Examiner Reports on Oxycodone-Related Deaths*. Accessed November 13, 2018 from https://web.archive.org/web/20130304035640/http://www.deadiversion.usdoj.gov/drugs_concern/oxycodone/oxycontin7.htm

[112] *See* n. 73 at p. 5.

The plain facts regarding the superior oral route of abuse for oxycodone—which is already known on the street, dating back at least to 2011[113,114]—demonstrates the pointlessness of attempting to label an oxycodone ADF formulation for either intranasal or intravenous abuse without addressing oral abuse. Despite this knowledge, FDA has continued to allow test subjects to be put at risk by approving unethical HAP studies.

5. Clinical Data Submitted by SpecGx LLC as Part of NDA 209774 Demonstrates no Evidence of Purported Abuse-Deterrent Properties

MNK-812 is claimed to possess abuse-deterrent properties for both the intranasal and intravenous routes of abuse. As described by FDA, "The abuse-deterrent properties of the drug product are imparted by excipients that act as gelling agents and potential nasal irritants."[115] However, SpecGx's own clinical studies show these properties are ineffective in preventing grinding, insufflation, and extraction of MNK-812.

When manipulated for particle size reduction, 90% of the resulting particles were of a size able to be insufflated: "MNK-812 (15 and 30 mg tablets) gave a maximum of approximately 90% of particles <500 microns with the use of readily-available mechanical tools. The measurement of 500 microns is specifically mentioned because this is roughly an insufflatable particle size."[116] Furthermore, when compared to Roxicodone, MNK-812 was found to have effectively the same intranasal abuse potential: "Based on the PK profiles of the two tampered products, the differences in concentration of oxycodone after IN administration does not appear to be clinically significant." and, "[i]n the intranasal abuse potential study, the plasma concentrations of oxycodone do not appear to be significantly different between IN MNK-812 tablets and IN Roxicodone tablets."[117] Lastly, MNK-812 can be extracted to high label claim at room temperature: "In general, large volume extractions in several but not all ingestible solvents led to comparable amounts of oxycodone recovery between MNK-812 and Roxicodone. With an extraction time of 2 hours or less in a variety of ingestible solvents of varying pH, approximately 80-90% of oxycodone hydrochloride will be released from intact or ground tablets at room temperature."[118] This evidence clearly demonstrates MNK-812 possesses no meaningful abuse-deterrent properties when compared to Roxicodone.

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[113] *Oxycodone insufflation bioavailability vs. oral bioavailability*. Bluelight, August 28, 2011. Accessed November 13, 2018 from http://bluelight.org/vb/threads/587232-Oxycodone-insufflation-bioavailability-vs-oral-bioavailability
[114] *Discussion in 'Opiates'*, April 2009. Accessed November 13, 2018 from https://www.hipforums.com/forum/threads/to-the-people-who-only-snort-oxycodone.336603/
[115] See n.24 at 100.
[116] Id. at 101.
[117] Id. at 98.
[118] Id. at 101.

IV. Public Impact – Opioid Morbidity and Mortality

As pain experts have explained, "[a]ddiction develops slowly, usually only after months of exposure, but once addiction develops, it is a separate, often chronic medical illness that will typically not remit simply with opioid discontinuation and will carry a high risk of relapse for years without proper treatment."[119] As such, abuse-deterrent opioids were originally approved and marketed to correct what is now known to be a flawed premise: that addiction was a consequence of abuse and misuse.[120] However, it is not the abuse of opioids that creates addicts; addiction causes abuse of opioids.

The United States is experiencing an iatrogenic opioid epidemic that continues to rage out of control. According to the CDC, "[s]ince 1999, the amount of prescription opioids sold in the U.S. nearly quadrupled, yet there has not been an overall change in the amount of pain that Americans report."[121] And, in 2016, there were over 42,000 deaths involving opioids, equivalent to 114 deaths per day.[122] The increase in deaths from opioid overdose is directly proportional to the increase in the volume of prescription opioids sold. The dramatic growth in overdose deaths can be seen in the following graph:

[119] Nora D. Volkow, M.D., and A. Thomas McLellan, Ph.D, *Opioid Abuse in Chronic Pain — Misconceptions and Mitigation Strategies*, N Engl J Med, March 31, 2016, p. 1256, accessed on November 13, 2018 from http://www.nejm.org/doi/full/10.1056/NEJMra1507771#t=article

[120] "When OxyContin entered the market in 1996, the FDA approved its original label, which stated that iatrogenic addiction was "very rare" if opioids were legitimately used in the management of pain." — Van Zee, Art. "The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy." American Journal of Public Health 99.2 (2009): 221–227. PMC. Web. 19 July 2017. Accessed November 13, 2018 from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2622774/

[121] Center for Disease Control and Prevention, *Understanding the Epidemic*, accessed November 13, 2018 from https://www.cdc.gov/drugoverdose/epidemic/

[122] Center for Disease Control and Prevention, *Opioid Overdose*, accessed November 13, 2018 from https://www.cdc.gov/drugoverdose/index.html

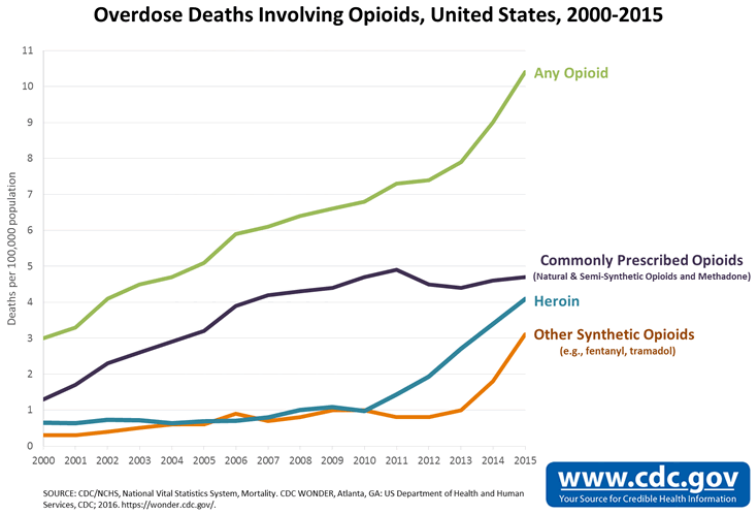

Figure 7 – Growth in overdose deaths involving opioids

Moreover, "prescription opioids continue to be involved in more overdose deaths than any other drug, and all the numbers are likely to underestimate the true burden given the large proportion of overdose deaths where the type of drug is not listed on the death certificate."[123]

Importantly, the CDC has observed that "[o]verdose risk increases in a dose–response manner, at least doubling at 50 to 99 morphine milligram equivalents (MME) per day and increasing by a factor of up to 9 at 100 or more MME per day, as compared with doses of less than 20 MME per day."[124] Accordingly, "1 of every 550 patients started on opioid therapy died of opioid-related causes a median of 2.6 years after the first opioid prescription; the proportion was as high as 1 in 32 among patients receiving doses of 200 MME or higher."[125] With strengths as high as 30 milligrams per tablet, the MNK-812 product has the potential to deliver 90 MME when dosed BID, and 270 MME when dosed every 4 hours—a total daily dose that is expected to increase the likelihood of addiction and death. The proposed labeling for NDA 209774 would also introduce additional risks to the public health, given the anticipated long-term duration of treatment when used for chronic pain. This is because the risk of continued opioid use is heavily dependent on the length of the patient's first opioid prescription, as measured in days. For

[123] Center for Disease Control and Prevention, *Opioid Data Analysis*, accessed November 13, 2018 from https://www.cdc.gov/drugoverdose/data/analysis.html
[124] *See* n. 15 at 1502-1503.
[125] *Id*. at 1503.

example, the CDC reports that the one- and three-year probabilities of continued opioid use positively correlate with the number of days' supply of the first opioid prescription:[126]

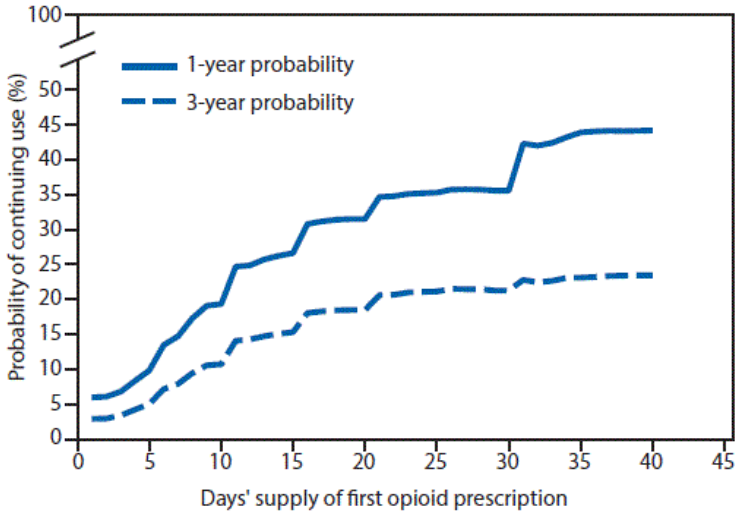

Figure 8 – Continued Opioid Use

CDC data suggests that the proposed labeling for NDA 209774, including use for the treatment of chronic pain, would continue to create new addicts and, thus, further contribute to the opioid epidemic.

Finally, former Director of the CDC, Dr. Thomas Frieden, M.D., M.P.H. and Debra Houry, M.D., M.P.H. have provided perhaps the best summary of the consequences of the use of opioids for the treatment of chronic pain:

> "Beginning in the 1990s, efforts to improve treatment of pain failed to adequately take into account opioids' addictiveness, low therapeutic ratio, and lack of documented effectiveness in the treatment of chronic pain."[127]
>
> "Whereas the benefits of opioids for chronic pain remain uncertain, the risks of addiction and overdose are clear."[128]
>
> "We know of no other medication routinely used for nonfatal conditions that kills patients so frequently."[129]

[126] Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use — United States, 2006–2015. MMWR Morb Mortal Wkly Rep 2017;66:265–269. Accessed November 13, 2018 from https://www.cdc.gov/mmwr/volumes/66/wr/pdfs/mm6610a1.pdf
[127] *See* n. 15 at 1501.
[128] *Id.* at 1502.
[129] *Id.* at 1503.

V. CONCLUSION

The root cause of the United States opioid epidemic is the FDA's approval of opioid drug products for the treatment of chronic pain absent substantial evidence of efficacy. Exacerbating the problem, the FDA-approved labeling provided the medical community with false reassurance that opioids are safe and effective in the treatment of chronic pain despite a lack of evidence to support such an indication. This led the medical community to change its long-held beliefs and practices about prescribing low-dose opiates only for acute injury and only for short durations due to severe risk of addiction and a lack of empirical data of efficacy for chronic pain.

Ultimately, the FDA's action to approve prescription opioids for chronic pain is in violation of the FD&C Act requirement that FDA have "substantial evidence consisting of adequate and well-controlled investigations." Since being wrongfully approved for treatment of chronic pain, it is estimated that opioids have killed over 200,000 people. [130] By approving opioids indicated for the treatment of chronic pain without substantial evidence of their efficacy for this indication, the FDA has helped to facilitate the launch of the U.S. opioid epidemic—an escalating public health crisis unprecedented in our country.

To address these concerns, PMRS requests that FDA refrain from approving any pending or future application for an opioid product submitted pursuant to section 505(b) or 505(j) of the FD&C Act, including NDA No. 209774 submitted by SpecGx LLC, with the proposed indication of "management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate," or with any other labeling that suggests that the product is appropriate for use in the treatment of chronic pain. PMRS further requests that FDA refrain from approving any pending or future application for an opioid product with abuse-deterrent labeling submitted pursuant to section 505(b) or 505(j) of the FD&C Act, including NDA No. 209774 submitted by SpecGx LLC, absent a meaningful demonstration of any such claims in compliance with a defined legal standard rather than mere reliance on methods unlawfully prescribed in the form of an FDA Guidance Document.

VI. INTERESTS OF PMRS, INC.

PMRS submitted a New Drug Application (NDA) on January 16, 2017 under Section 505(b)(2) of the FD&C Act for Oxycodone HCl IR ADF capsules with a proposed indication for the management of acute pain severe enough to require an opioid analgesic and for which alternative

[130] National Institute on Drug Abuse (NIDA), *Overdose Death Rates*, accessed November 13, 2018 from https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates

treatments are inadequate. PMRS' proposed product is intended only for use in the management of acute pain and is not labeled for chronic use. In addition, to PMRS' knowledge, its NDA is the first application submitted to FDA with labeling that adheres to the CDC's recommendations for maximum daily dose (in morphine milligram equivalents per day) and duration of treatment. The product's package insert is proposed to include a statement informing physicians that the drug is formulated with inactive ingredients intended to make the capsule more difficult to manipulate for abuse, and that postmarketing epidemiology studies are required to demonstrate meaningful abuse-deterrent properties. Oxycodone HCl IR ADF capsules should be prescribed knowing abuse-deterrent properties have not been demonstrated.

B. ENVIRONMENTAL IMPACT

Petitioner claims a categorical exclusion from the requirements of an environmental assessment or environmental impact statement pursuant to 21 C.F.R. § 25.31.

C. ECONOMIC IMPACT

An economic impact statement will be submitted if requested by the Commissioner, pursuant to 21 C.F.R. § 10.30(b).

D. CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: April 10, 2014. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Pharmaceutical Manufacturing Research Services, Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully Submitted,

Edwin R. Thompson, President
Pharmaceutical Manufacturing Research Services, Inc.
202 Precision Road
Horsham, PA 19044