IN THE DISTRICT COURT OF CLEVELAND COUNTY
STATE OF OKLAHOMA

STATE OF OKLAHOMA, ex rel., MIKE HUNTER, ATTORNEY GENERAL OF OKLAHOMA, Plaintiff, v. PURDUE PHARMA L.P., *et al.*, Defendants.	Case No. CJ-2017-816 Judge Thad Balkman William C. Hetherington Special Discovery Master

DEFENDANTS JANSSEN PHARMACEUTICALS, INC. AND JOHNSON & JOHNSON'S MOTION *IN LIMINE* NO. 10 TO EXCLUDE THE 2004 FDA WARNING LETTER

REDACTED VERSION

THIS DOCUMENT WAS FILED IN ITS ENTIRETY APRIL 26, 2019,
UNDER SEAL
PER COURT ORDER DATED APRIL 16, 2018

Defendants Janssen Pharmaceuticals, Inc. ("Janssen")[1] and Johnson & Johnson ("J&J"), hereby move this Court for an order excluding from trial any evidence, reference, or argument related to the September 2, 2004 FDA Warning Letter. Such statements should be excluded because they are impermissible hearsay and are unfairly prejudicial. *See* 12 O.S. §§ 2403, 2801-2803. Janssen and J&J accordingly respectfully request that their Motion *in Limine* be granted, and for such other relief as the Court deems just and proper.

BRIEF IN SUPPORT

In support of this Motion *in Limine*, Janssen and J&J show the following:

I. INTRODUCTION

The State intends to invoke a 2004 Warning Letter issued by the FDA regarding a Duragesic informational "file card" to show that Janssen engaged in misleading marketing. That effort betrays a fundamental misunderstanding of FDA warning letters. Far from conclusive determinations of wrongdoing, warning letters are preliminary, informal measures designed to promote dialogue and secure voluntary changes in marketing by regulated companies. Allowing the State to broadcast the false suggestion that the 2004 Warning Letter conclusively found Janssen's marketing to be misleading risks severely prejudicing Janssen in related cases. Indeed, the State cannot present the letter for *any* purpose, because, as the Arkansas Supreme Court has recognized, such letters are inadmissible hearsay.

II. BACKGROUND

The FDA's Division of Drug Marketing, Advertising, and Communications sent Janssen a Warning Letter on September 2, 2004. Ex. A, 2004 Warning Letter. The letter challenged

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[1] "Janssen" also refers to Janssen Pharmaceuticals, Inc.'s predecessors, Ortho-McNeil-Janssen Pharmaceuticals, Inc. and Janssen Pharmaceutica, Inc.

statements Janssen made in a "file card"—a three-by-five-inch informational aid—that Janssen sales representatives used between August 2003 and September 2004. *Id*; Ex. B, File Card (DR-850).

More specifically, the Warning Letter objected to the file card's use of data from the Drug Abuse Warning Network ("DAWN") to support the suggestion "that Duragesic is less abused than other opioid drugs." Ex. A, 2004 Warning Letter at 2. The letter reasoned that "DAWN is not a clinical trial database" and therefore could not "provide the basis for a valid comparison among [] products." *Id.* at 2. It also challenged evidence cited as support for claims about Duragesic's efficacy and side effects. *Id.* at 2-3. [redacted]

III. ARGUMENT

A. An FDA Warning Letter Is Not A Final Agency Determination Of Improper Marketing

Warnings letters are a preliminary and informal alternative to the FDA's power to bring a formal enforcement action. The FDA issues warning letters for "violations of regulatory

significance ... that *may* actually lead to an enforcement action[.]" Regulatory Procedures Manual § 4.1-1-1 (Sept. 2018) (emphasis added).[2] But as the agency's procedures manual explains, a "Warning Letter is informal and advisory" only. *Id.* It "communicates the Agency's position on a matter, [but] it does not commit FDA to taking enforcement action." *Id.* Through warning letters, the FDA initiates dialogue with the regulated company to achieve "voluntary compliance." *Id.*

Of particular significance here, the FDA "does not consider Warning Letters to be final Agency action on which it can be sued." *Id.* Indeed, FDA regulations specifically provide that mere "correspondence" is not "final administrative action." 21 C.F.R. § 10.65(a). And courts have followed suit by holding that warning letters—including the very 2004 Warning Letter at issue here—are not final agency determinations of legal or regulatory violations.

In *State ex rel. McGraw v. Johnson & Johnson*, 704 S.E. 2d 677 (W. Va. 2010), West Virginia sued Johnson & Johnson and Janssen under a state consumer protection statute, arguing that the Duragesic file card communicated false or misleading information to health care providers. *Id.* at 681. West Virginia's theory was that the 2004 Warning Letter constituted a preclusive legal determination that statements in the file card were false and misleading. *Id.* at 687. The Supreme Court of Appeals rejected that theory and refused to give the 2004 Warning Letter preclusive effect. Emphasizing their "informal and advisory nature"—and their purpose of promoting voluntary compliance instead of committing the agency to formal enforcement action—the court concluded that Warning Letters are only "preliminary notification[s]" rather than "quasi-judicial determinations by the FDA." *Id.* at 689.

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[2] Available at https://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM074330.pdf (accessed Apr. 26, 2019). The version of the Regulatory Procedures Manual in effect at the time of the 2004 Warning Letter had the same operative language. *See State ex rel. McGraw v. Johnson & Johnson*, 704 S.E.2d 677, 688 (W. Va. 2010) (quoting March 2004 Regulatory Procedures Manual).

An unbroken string of precedent confirms the result in *McGraw*. Every court to consider the issue has concluded that "FDA warning letters do not represent final agency action subject to judicial review." *Holistic Candlers & Consumers Ass'n v. Food & Drug Admin.*, 664 F.3d 940, 944-45 (D.C. Cir. 2012); *accord Regenerative Scis., Inc. v. U.S. Food And Drug Admin.*, 2010 WL 1258010, at *7 (D. Colo. Mar. 26, 2010); *Schering-Plough Healthcare Prod., Inc. v. Schwarz Pharma, Inc.*, 547 F. Supp. 2d 939, 947 (E.D. Wis. 2008); *Professionals and Patients for Customized Care v. Shalala*, 847 F. Supp. 1359, 1365 (S.D. Tex. 1994).

B. The 2004 Warning Letter Should Be Excluded As Hearsay

The informal and preliminary nature of the 2004 Warning Letter renders it impermissible hearsay for the purpose of establishing the truth of the matter the State contends it asserted: that Janssen engaged in misleading marketing. 12 O.S. §§ 2801, 2802. While certain public records and reports fall within an exception to the hearsay rule, 12 O.S. § 2803(8), that exception expressly does not cover "factual findings resulting from special investigation of a particular complaint, case or incident," *id.* § 2803(8)(d). Applying similar language in the Arkansas Rules of Evidence, *see* Ark. R. Evid. 803(8), and pointing to the "informal and advisory" nature of warning letters, the Arkansas Supreme Court held that an FDA warning letter arose from just such a "special investigation of a particular complaint, case, or incident" and was therefore inadmissible. *Ortho-Ortho-McNeil-Janssen Pharm., Inc. v. State*, 432 S.W.3d 563, 579 (Ark. 2014). Oklahoma law is the same, *see* 12 O.S. § 2803(8), and so the 2004 Warning Letter must be excluded as inadmissible hearsay. *See Broadcast Music, Inc. v. Xanthas, Inc.*, 855 F.2d 233, 238 (5th Cir. 1988) (hearsay not admissible in bench trial).

C. Evidence Regarding The 2004 Warning Letter Should Be Excluded Because It Is Prejudicial To Janssen

While the FDA's own guidelines and unanimous judicial precedent teach that a Warning Letter is a preliminary measure designed to encourage voluntary changes to marketing materials, [redacted] Janssen's Motion *in Limine* should also be granted because such evidence would cause it severe undue prejudice.

Falsely branding a defendant as a lawbreaker is just the sort of prejudicial testimony that Rule 2403 is intended to bar. *See Sykes v. State*, 1951 OK CR 14, 238 P.2d 384, 387 (reference to defendant as a "criminal" was unfairly prejudicial). Suggesting that the Warning Letter embodies the FDA's expert finding of false marketing—when it is in truth only a "preliminary notification" meant to kick-start a dialogue, *McGraw*, 704 S.E. 2d at 689—is equally misleading and prejudicial. Janssen has never been charged with any crime in connection with its opioid medications, and the FDA has never conclusively deemed any of its promotions of those medicines to be misleading. But the State would have this Court and the public conclude otherwise.

The Warning Letter is all the more prejudicial because it carries the imprimatur of a respected federal agency. The Arkansas Supreme Court concluded that the admission of an FDA warning letter was unduly prejudicial because "[r]eports issued by governmental agencies" "may well carry inordinate weight" due to "their 'official' nature." *Ortho-McNeil-Janssen Pharm., Inc.*, 432 S.W.3d at 579 (quoting *Boude v. Union Pac. R. Co.*, 277 P.3d 1221, 1225 (Mont. 2012)). Other courts have not hesitated to exclude evidence about preliminary agency actions on the ground that their prejudicial effect outweighs their limited probative value. *See, e.g., Johnson v. Ford Motor Co.*, 988 F.2d 573, 580 (5th Cir. 1993) (affirming exclusion of NHTSA

correspondence in part because "the 'official' nature of the inquires could have misled the jury"); *Kociemba v. G.D. Searle & Co.*, 683 F. Supp. 1582 (D. Minn. 1988) (holding that an FDA task force report critical of laboratory procedures should be excluded under Federal Rule of Evidence 403); *Fowler v. Firestone Tire & Rubber Co.*, 92 F.R.D. 1 (N.D. Miss. 1980) (holding that an NHTSA report's prejudicial impact outweighed its probative value where it was an investigatory report conducted without any adversarial proceeding). Those principles should preclude the State from blasting the public with false assertions that the FDA conclusively found Janssen's marketing to be misleading—the agency's informal and preliminary position simply cannot support such a claim.

Though some courts hold prejudice exclusions to be unnecessary in bench trials, *see, e.g.*, *United States v. Kienlen,* 349 F. App'x 349, 351 (10th Cir. 2009), those decisions have little application here where the concern is not about the judge in this case, but about exposing prejudicial information to millions of Americans, including countless prospective jurors in hundreds of matters pending against Janssen and J&J across the country. The prejudice from these statements will not stop at the courthouse steps; it will infect each and every subsequent opioid-related trial. The Court should therefore bar any such evidence. *See State v. Miller*, 165 A.2d 829, 831 (N.J. App. Div. 1960) ("Even in a trial without jury, a defendant should not be required to contend with inadmissible evidence, where it appears that it may have a prejudicial effect.").

IV. CONCLUSION

For all these reasons, the Court should grant Janssen and J&J's Motion *in Limine* and issue an order barring the State from introducing any evidence, reference, or argument related to the September 2, 2004 FDA Warning Letter.

Dated: April 26, 2019

Respectfully submitted,

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CERTIFICATE OF MAILING

Pursuant to Okla. Stat. tit. 12, § 2005(D), and by agreement of the parties, this is to certify on April 26, 2019, a true and correct copy of the above and foregoing has been served via electronic mail, to the following:

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EXHIBIT A

File Provided Natively

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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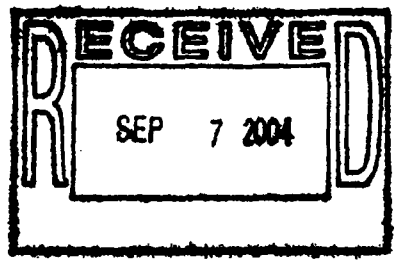

TRANSMITTED BY FACSIMILE

Ajit Shetty, M.D.
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Janssen Pharmaceutica, Inc.
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RE: NDA # 19-813
Duragesic® (fentanyl transdermal system) CII
MACMIS # 12386

WARNING LETTER

Dear Dr. Shetty,

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional file card (DR-850) for Duragesic® (fentanyl transdermal system) submitted by Janssen Pharmaceutica, Inc. (Janssen) under cover of Form FDA 2253. The file card makes false or misleading claims about the abuse potential and other risks of the drug, and includes unsubstantiated effectiveness claims for Duragesic The file card thus misbrands the drug under Section 502(a) of the Federal Food, Drug, and Cosmetic Act (Act) 21 U.S.C. 352(a). By suggesting that Duragesic has a lower potential for abuse compared to other opioid products, the file card could encourage the unsafe use of the drug, potentially resulting in serious or life-threatening hypoventilation.

Background

According to the approved product labeling (PI), Duragesic is a transdermal system providing continuous systemic delivery of fentanyl, a potent opioid analgesic, for 72 hours. Duragesic is indicated in the management of chronic pain in patients who require continuous opioid analgesia for pain that cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids. The Indications and Usage section of the PI states: "Duragesic should not be used in the management of acute or postoperative pain because serious or life-threatening hypoventilation could result (see BOX WARNING and CONTRAINDICATIONS)." The boxed warning and contraindications sections further discuss the risk of serious or life-threatening hypoventilation. This risk is also addressed in the warnings and precautions sections of the PI.

Duragesic has the potential for abuse. The Drug Abuse and Dependence section of the PI states, in pertinent part:

> Fentanyl is a Schedule II controlled substance and can produce drug dependence similar to that produced by morphine. DURAGESIC® (fentanyl transdermal system) therefore has the

potential for abuse Tolerance, physical and psychological dependence may develop upon repeated administration of opioids.

False or Misleading Safety Claims

The file card presents the prominent claim, "Low reported rate of mentions in DAWN data," along with Drug Abuse Warning Network (DAWN) data comparing the number of mentions for Fentanyl/combinations (710 mentions) to other listed opioid products, including Hydrocodone/combinations (21,567 mentions), Oxycodone/combinations (18,409 mentions), and Methadone (10,725 mentions). The file card thus suggests that Duragesic is less abused than other opioid drugs.

This is false or misleading for two reasons. First, we are not aware of substantial evidence or substantial clinical experience to support this comparative claim The DAWN data cannot provide the basis for a valid comparison among these products. As you know, DAWN is not a clinical trial database. Instead, it is a national public health surveillance system that monitors drug-related emergency department visits and deaths. If you have other data demonstrating that Duragesic is less abused, please submit them.

Second, Duragesic is not as widely prescribed as other opioid products. As a result, the relatively lower number of mentions could be attributed to the lower frequency of use, and not to a lower incidence of abuse. The file card fails to disclose this information.

The information from the Drug Abuse and Dependence section of the PI, which appears in a footnote on the opposite page of the spread (entitled "Favorable side-effect profile") is not sufficient to make the claim truthful and non-misleading. The footnote does not substantiate the claim. Nor does it set forth qualifying information about the frequency of prescribing of the compared opioids.

In addition, on the page entitled "Favorable side-effect profile," the file card presents the claim, "Minimizes the potential for local GI side effects by avoiding GI absorption," along with a table entitled, "Adverse experiences in patients with cancer," that shows a 14 percent rate of constipation with Duragesic and a 0 percent discontinuation rate because of constipation. This combination of text and graphics is false or misleading, in that it suggests that Duragesic is associated with less constipation, nausea, and vomiting than oral opioids, which are absorbed by the GI tract. We are not aware of substantial evidence or substantial clinical experience to support this comparative claim.

Unsubstantiated Effectiveness Claims

The file card states, on page four, "Demonstrated effectiveness in chronic back pain with additional patient benefits." The referenced study,[1] conducted by Simpson et al., is inadequate to support this claim, because it was an open-label, single-arm trial with no control group. We are not aware of substantial evidence or substantial clinical experience to support this claim.

On pages 4 and 5, the file card includes the claims, "86% of patients experienced overall benefit in a clinical study based on: pain control, disability in ADLs, quality of sleep," "All patients who experienced overall benefit from DURAGESIC would recommend it to others with chronic low back

[1] Simpson RK Jr, Edmondson EA, Constant CF, Collier C. Transdermal fentanyl as treatment for chronic low back pain. J Pain Symptom Manage 1997, 14.218-224

pain," "Significantly reduced nighttime awakenings," and "Significant improvement in disability scores as measured by the Oswestry Disability Questionnaire and Pain Disability Index" To support these claims, the file card again cites the Simpson et al trial For the reasons noted above, this uncontrolled study is inadequate to support such claims We are not aware of substantial evidence or substantial clinical experience to support these claims

On pages 6 and 7, the file card includes the claims, "Long-term effects 12-month open-label study," "Significant improvement in physical functioning summary score," and "Significant improvement in social functioning," along with figures illustrating these claims. To support these claims, the file card cites a study[2] conducted by Milligan et al. This open-label, uncontrolled study is not adequate in design to show an analgesic effect. The data from this study are not substantial evidence or substantial clinical experience to support such outcomes claims. We are not aware of substantial evidence or substantial clinical experience to support these claims.

On pages 8 and 9, the file card includes the claims, "Improved patient outcomes: Open-label, crossover comparison study," "Significant improvement in physical functioning summary score," and "Significant improvement in social functioning," along with figures comparing data for Duragesic and sustained release oral morphine. To support these claims, the file card cites the study[3] conducted by Allan et al.. An open-label study cannot minimize bias in the reporting of subjective response in the SF-36, a general healthcare questionnaire. It is therefore not sufficient to support the cited claims. We are not aware of substantial evidence or substantial clinical experience to support these claims.

Finally, the file card prominently presents the claims, "1,360 loaves...and counting," "Work, uninterrupted," "Life, uninterrupted," "Game, uninterrupted," "Chronic pain relief that supports functionality," "Helps patients think less about their pain," and "Improvements in physical and social functioning." These outcome claims are misleading because they imply that patients will experience improved social or physical functioning or improved work productivity when using Duragesic. Janssen has not provided references to support these outcome claims We are not aware of substantial evidence or substantial clinical experience to support these claims.

Conclusions and Requested Actions

The file card makes false or misleading safety claims and unsubstantiated effectiveness claims for Duragesic. The file card thus misbrands Duragesic in violation of the Act 21 U.S.C § 352(a).

DDMAC requests that Janssen immediately cease the dissemination of promotional materials for Duragesic the same as or similar to those described above. Please submit a written response to this letter on or before September 17, 2004, describing your intent to comply with this request, listing all promotional materials for Duragesic the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a plan of action to disseminate truthful, non-misleading, and complete information to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug

[2] Milligan K, Lanteri-Minet M, Borchert K, et al. Evaluation of long-term efficacy and safety of transdermal fentanyl in the treatment of chronic noncancer pain. J Pain 2001,2:197-204

[3] Allan L, Hays H, Jensen N-H, et al Radomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain BMJ 2001,322 1154-1158

Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857, facsimile at 301-594-6771 In all future correspondence regarding this matter, please refer to MACMIS # 12386 in addition to the NDA numbers. We remind you that only written communications are considered official

The violations discussed in this letter do not necessarily constitute an exhaustive list It is your responsibility to ensure that your promotional materials for Duragesic comply with each applicable requirement of the Act and FDA implementing regulations

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Abrams
9/2/04 04:32:52 PM

EXHIBIT B

[FILED UNDER SEAL]

EXHIBIT C

[FILED UNDER SEAL]

EXHIBIT D

[FILED UNDER SEAL]

EXHIBIT E

[FILED UNDER SEAL]