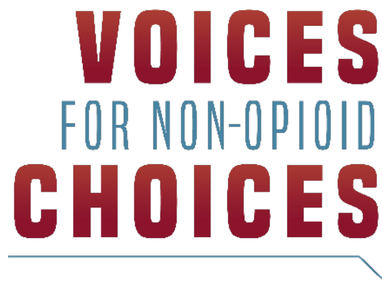

April 11, 2022

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Submitted online via www.regulations.gov.

RE: FDA-2021-N-0556: Development of Non-Opioid Analgesics for Acute Pain: Guidance for Industry

To Whom It May Concern:

Thank you for the opportunity to provide insights into the draft guidance on "Development of Non-Opioid Analgesics for Acute Pain," as published in the *Federal Register* on February 10, 2022. Our comments will focus on the benefits of non-opioid analgesic products generally and highlight barriers that currently exist that inhibit patient and provider access to these products. Specifically, we believe that the greatest impediment to more robust innovation and development of non-opioid analgesics is the fact that the use of such products is often disincentivized by current reimbursement policies.

Voices for Non-Opioid Choices ("Voices") – and our more than 80 national and state partners – shares the Food and Drug Administration's (FDA) commitment to combatting the nation's opioid crisis. This includes advancing measures that can decrease unnecessary patient exposure to opioid analgesics. In doing so, we can prevent new cases of addiction and opioid use disorder.

Voices was launched in 2019 around the shared commitment to preventing opioid addiction through increased access to and use of non-opioid pain management approaches for acute pain patients. At the time, the opioid epidemic looked far different – in 2018, we lost 115 Americans every day, on average, to an opioid-related drug overdose[1]. Now, we lose approximately 217

[1] Substance Abuse and Mental Health Services Administration (US); Office of the Surgeon General (US). Facing Addiction in America: The Surgeon General's Spotlight on Opioids [Internet]. Washington (DC): US Department of Health and Human Services; 2018 Sep. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538436/

Americans every day to an opioid-related drug overdose – a 90 percent increase in just four short years[2].

Voices agrees with the draft guidance's assessment of the potential risks of unnecessary patient exposure to opioids. The guidance notes, "exposure to an opioid analgesic presents a risk of addiction, misuse, or abuse. In addition to the risk of addiction, opioid use may also cause serious adverse reactions, including overdose, and death.[3]" Data from the Substance Abuse and Mental Health Services Administration (SAMSHA) suggests that 80 percent of heroin users initiated their habit via prescription opioid pills[4].

Opioid-based pain relief remains the standard of care for surgery patients in the United States. Some estimates note that more than 90 percent of surgery patients receive some level of opioid-based pain relief[5]. Frequently, these patients are prescribed more than 80 pills to manage postsurgical pain[6]. As a result, it is not surprising to see more than 3 million Americans initiate long-term opioid use every year following a surgical procedure[7]. This represents just less than 10 percent of all outpatient surgery patients in any given year[8].

Benefits of Non-Opioid Approaches to Acute Pain

Non-opioid pain management approaches offer a number of clinical benefits, including:

- Reducing unnecessary patient exposure to opioids;

The draft guidance correctly notes that one of the principal endpoints associated with administering non-opioid pain management approaches is "reducing or eliminating opioid use." The peer-reviewed literature supports the notion that non-opioids offer the opportunity to substantially reduce post-surgical opioid consumption, including:

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[2] Ahmad FB, Rossen LM, Sutton P. Provisional drug overdose death counts. National Center for Health Statistics. 2021. https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

[3] Food and Drug Administration (2021). Development of Non-Opioid Analgesics for Acute Pain; Draft Guidance for Industry. Line 290-292. *Federal Register.* https://www.federalregister.gov/documents/2022/02/10/2022-02858/development-of-non-opioid-analgesics-for-acute-pain-draft-guidance-for-industry-availability

[4] Center for Behavioral Health Statistics and Quality (CBHSQ). Table 7.50A. 2014 National Survey on Drug Use and Health: Detailed Tables. Substance Abuse and Mental Health Services Administration, Rockville, MD; 2015

[5] Hill, M. V., McMahon, M. L., Stucke, R. S., & Barth, R. J., Jr (2017). Wide Variation and Excessive Dosage of Opioid Prescriptions for Common General Surgical Procedures. Annals of surgery, 265(4), 709–714. Available at: https://doi.org/10.1097/SLA.0000000000001993.

[6] Bicket M, et al. (2017). Prescription opioid oversupply following orthopedic surgery: A prospective cohort study. American Pain Society annual scientific meeting 2017. https://www.jpain.org/article/S1526-5900(17)30157-8/pdf.

[7] Hah, J. M., Bateman, B. T., Ratliff, J., Curtin, C., & Sun, E. (2017). Chronic Opioid Use After Surgery: Implications for Perioperative Management in the Face of the Opioid Epidemic. Anesthesia and analgesia, 125(5), 1733–1740. Available at: https://doi.org/10.1213/ANE.0000000000002458.

[8] *Ibid.*

- One study that found the use of non-opioid pain approaches reduced opioid consumption by 91 percent within 24 hours following total knee arthroplasty (TKA)[9];
- A study looking at third molar extraction found that patients receiving non-opioid pain management support were prescribed 59 percent fewer opioids[10]; and
- An analysis of total hip arthroplasty (THA) patients who received non-opioid pain approaches consumed 73 percent fewer opioids three days following their procedure[11].

- Providing comparable (or better) analgesic support to traditional approaches; and

Despite the fact that opioid-based pain treatments remain the standard of care, non-opioid pain approaches can provide comparable – or better – analgesic support for patients, considering:

- One study evaluating the impact of a breast surgery focused enhanced recovery after surgery (ERAS) protocol in lumpectomy procedures found that non-opioid based pain management support was just as effective as the standard of care[12]; and
- Colorectal patients receiving non-opioid pain management support reported significantly lower pain scores after surgery – in one study, these patients reported pain scores that were 17 percent lower than patients receiving opioids[13].

- Reducing opioid-related adverse events (ORAE) and rehospitalizations.

Opioids themselves carry specific therapeutic complications to patients. These challenges extend beyond potential risk for long-term use after initial exposure. These complications can

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[9] Dysart, S. H., Barrington, J. W., Del Gaizo, D. J., Sodhi, N., & Mont, M. A. (2019). Local Infiltration Analgesia With Liposomal Bupivacaine Improves Early Outcomes After Total Knee Arthroplasty: 24-Hour Data From the PILLAR Study. The Journal of arthroplasty, 34(5), 882–886.e1. Available at: https://doi.org/10.1016/j.arth.2018.12.026.

[10] Lieblich, S. E., Misiek, D., Olczak, J., Fleck, H., & Waterman, F. (2021). A Retrospective Cross-Sectional Study of the Effect of Liposomal Bupivacaine on Postoperative Opioid Prescribing After Third Molar Extraction. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons, 79(7), 1401–1408.e1. Available at: https://doi.org/10.1016/j.joms.2021.02.012.

[11] Asche, C. V., Ren, J., Kim, M., Gordon, K., McWhirter, M., Kirkness, C. S., & Maurer, B. T. (2017). Local infiltration for postsurgical analgesia following total hip arthroplasty: a comparison of liposomal bupivacaine to traditional bupivacaine. Current medical research and opinion, 33(7), 1283–1290. Available at: https://doi.org/10.1080/03007995.2017.1314262.

[12] Stratton, M., Waite, P. D., Powell, K. K., Scopel, M. M., & Kukreja, P. (2021). Benefits of the enhanced recovery after surgery pathway for orthognathic surgery. International journal of oral and maxillofacial surgery, S0901-5027(21)00161-2. Advance online publication. Available at: https://doi.org/10.1016/j.ijom.2021.04.008.

[13] Beck, D. E., Margolin, D. A., Babin, S. F., & Russo, C. T. (2015). Benefits of a Multimodal Regimen for Postsurgical Pain Management in Colorectal Surgery. The Ochsner journal, 15(4), 408–412.

range in scope and impact from digestive challenges[14] (e.g., nausea, vomiting, and/or constipation) to respiratory depression[15].

In some instances, patients require continued hospital supervision or are readmitted to hospitals following an ORAE. Accordingly, one benefit of increased utilization of non-opioid pain management approaches is reducing the number of ORAEs associated with prescribing opioids to manage patients' pain.

The literature on the topic is clear and compelling that using ERAS and multimodal protocols is an effective way to limit ORAEs in surgical patients. Examples include:

- A study examining the dangers of opioid-based pain therapy among elderly Americans who are at increased risk of suffering from an ORAE after surgery[16]; and
- Another study that demonstrated that ORAEs rates are more than 50 percent lower in patients receiving multimodal pain management approaches[17].

Barriers Inhibiting Patient and Provider Access to Non-Opioid Therapies

Current Medicare reimbursement policy inadvertently incentivizes the use of opioid-based pain therapy. This is largely attributable to the fact that opioid-based pain relief is inexpensive but also because of the way that Medicare pays for surgical procedures.

Specifically, Medicare provides a single, bundled payment that is used to pay for a surgical procedure or a hospital stay. This payment is used to pay for the surgeons who perform the procedure, the nurses who assist, and any other supplies used during the procedure. This payment model creates incentives for facilities to lower the cost of these procedures, making them more profitable and helping lower overall healthcare costs.

Unfortunately, this payment only applies to those items and services for that patient while they are in the hospital. This would include any non-opioid-based treatment that would be given to the patient pre-, peri-, or postoperatively. As a result, these additional products and services increase the cost of the procedure to the facility. Opioids, on the other hand, are frequently

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[14] Stratton, M., Waite, P. D., Powell, K. K., Scopel, M. M., & Kukreja, P. (2021). Benefits of the enhanced recovery after surgery pathway for orthognathic surgery. International journal of oral and maxillofacial surgery, S0901-5027(21)00161-2. Advance online publication. Available at: https://doi.org/10.1016/j.ijom.2021.04.008.
[15] Radke, J. B., Owen, K. P., Sutter, M. E., Ford, J. B., & Albertson, T. E. (2014). The effects of opioids on the lung. Clinical reviews in allergy & immunology, 46(1), 54–64. Available at: https://doi.org/10.1007/s12016-013-8373-z.
[16] Halaszynski T. (2013). Influences of the aging process on acute perioperative pain management in elderly and cognitively impaired patients. The Ochsner journal, 13(2), 228–247.
[17] Yalmanchili, H. M., Buchanan, S. N., Chambers, L. W., Thorns, J. D., McKenzie, N. A., Reiss, A. D., Page, M. P., Dizon, V. V., Brooks, S. E., Shaffer, L. E., Lovald, S. T., Hartranft, T. H., & Price, P. D. (2019). Postlaparotomy pain management: Comparison of patient-controlled analgesia pump alone, with subcutaneous bupivacaine infusion, or with injection of liposomal bupivacaine suspension. Journal of opioid management, 15(2), 169–175. Available at: https://doi.org/10.5055/jom.2019.0498.

dispensed and given to patients upon discharge. This means that there is a separate payment – under Medicare Part D – covering the use of prescribed opioids. This payment system greatly incentivizes the use of opioid-based pain relief.

As a result, and without additional market demand for non-opioid pain therapies, there is little incentive for industry to continue to innovate and bring new, innovative therapies to market. While we applaud the steps the FDA is taking to provide guidance for industry on a clear pathway for developing safe and effective non-opioids, we are concerned that if Medicare payment policy fails to evolve, patients will miss out on potential innovation.

To address this, we need to redesign payment policy to create the necessary incentives for using non-opioid pain therapies. Doing so would not dictate or mandate clinical practice. Rather, it would pay for all pain management approaches – opioid-based and non-opioid based – the same way. It would treat all pain management protocols equally and let patients and providers make informed decisions on how they choose to manage acute pain.

Realigning this incentive structure would also recognize the current opioid crisis in the United States, help prevent opioid addiction, and save lives.

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Thank you for your consideration of these comments. We look forward to an ongoing dialogue with you and your colleagues, particularly on how we might partner on our shared commitment to prevent opioid addiction in the United States.

Sincerely,

Chris Fox
Executive Director