April 11, 2022

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

Re: Docket No. FDA–2021-N-0556: Development of Non-Opioid Analgesics for Acute Pain

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding the Draft Guidance on **Development of Non-Opioid Analgesics for Acute Pain.**

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO appreciates the Agency's efforts to develop draft guidance on non-opioid analgesics for acute pain. With the withdrawal of previous guidance on drug development for treatment of pain, the Agency left a policy void manifesting as uncertainty and risk for drug developers in this space. BIO looks forward to continuing to work with the Agency to achieve its stated priority of "fostering the development of novel non-opioid analgesics."[1]

BIO has several recommendations to improve the draft guidance:

Considerations for a General Acute Pain Indication

BIO recommends that the Agency prioritize implementation of policy that promotes efficient and effective development of non-opioid analgesics that support a general acute pain indication. Due to commercial, unmet need, and other practical drug development considerations, specific acute pain indications do not track to general clinical practice and may disincentivize sponsors from developing non-opioid analgesics. Given the current understanding of the biology of pain, BIO strongly encourages the Agency to articulate a regulatory path for the timely and efficient development of non-opioid analgesics pursuing a general acute pain indication.

Novel Mechanism of Action

With the impact of the opioid epidemic and urgency for non-opioid alternatives to address the unmet needs in the treatment of pain, BIO is concerned that FDA is setting a higher bar for the development of analgesics with novel mechanisms of action (MoA) than previous policy by stating a likely requirement for "clinical trials in more than two different pain populations to support a general acute pain indication." BIO recommends that the Agency clarify its intent to

[1] https://www.fda.gov/news-events/press-announcements/fda-takes-steps-aimed-fostering-development-non-addictive-alternatives-opioids-acute-pain-management

use MoA of the drug as the primary determinant of the evidentiary standard for efficacy (i.e., number of pivotal studies). Use of MoA as the primary determinant is undermined if the novel analgesic molecule has more than one MoA. For example, a current novel novel non-opioid molecule under development for pain may affect multiple pain pathways. Use of MoA as the determinant would confuse rather than clarify the evidentiary standard whereas adequate and well-controlled studies in a soft-tissue and hard-tissue would clearly demonstrate efficacy.

This is also a change from FDA's previous policy for the basis of approval and contrary to regulatory precedent of two models in nociceptive pain to be sufficient for demonstration of efficacy for a general acute pain indication, and is not rooted in sound science as a general proposition. Specifically, the new analgesics Nucynta (2008) and Olinvyk (2020) were approved for general pain indications on the basis of two pivotal trials in nonciceptive pain models. In 2015, FDA also approved a labeling supplement for Exparel that "made certain changes to the EXPAREL label in order to clarify that its indication was not limited to bunionectomy and hemorrhoidectomy procedures,"[2] when the two clinical trials establishing the product's efficacy studied only patients who underwent bunionectomies and hemorrhoidectomies (respectively).[3] The analgesics (Opioid or NSAID) approved by FDA for general acute pain in the past few decades have demonstrated that the two successful trials in nociceptive pain, one in hard tissue (e.g., bunionectomy) and one in soft tissue (e.g., abdominoplasty or hemorrhoidectomy) are sufficient to establish efficacy, not only in the two conditions studied but also for use to treat acute pain more generally.

Departing from this approach would result in future applicants being treated differently from applicants whose products have already been approved, and the new draft guidance does not specify a scientific rationale for its proposal to do so. This raises issues of fairness and administrative law based on the disparate treatment.[4] Moreover, the draft guidance does not articulate a rationale for distinguishing the number of pain populations to be studied on the basis of whether a product's mechanism of action is "well-established" or "novel," nor does the draft guidance explain the Agency's scientific basis for concluding that studying more than two pain populations is the appropriate threshold to establish a product's efficacy for a general acute pain indication when the mechanism of action is novel. The proposed approach is not grounded in the science as a general operating principle. For example, a product may demonstrate efficacy in inhibiting a novel target validated for pain treatment broadly such that studying the product's use in more than two pain populations should be unnecessary to support a general acute pain indication. Indeed, establishing an unnecessarily high threshold for supporting a general acute pain indication could discourage the development of novel analgesic drugs for such uses, contrary to the goals of the SUPPORT Act and FDA's draft guidance.

Requiring clinical trials in more than two different pain populations would also be in tension with the statutory standard for establishing substantial evidence of a drug's effectiveness—two adequate and well-controlled clinical investigations or, alternatively in some circumstances, one

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[2] Letter from Dr. Janet Woodcock, Director for the Center for Drug Evaluation and Research, to Mr. David Stack, Chief Executive Officer and Chairman of Pacira Pharmaceuticals, Inc. 2 (Dec. 14, 2015), https://www.fda.gov/media/95042/download.

[3] Exparel Prescribing Information, Section 14: Clinical Studies (rev. Dec. 2015), https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022496s019lbl.pdf.

[4] *See Bracco Diagnostics, Inc. v. Shalala,* 963 F. Supp. 20, 28 (D.D.C. 1997) ("The disparate treatment of functionally indistinguishable products is the essence of the meaning of arbitrary and capricious.").

adequate and well-controlled clinical investigation supplemented by confirmatory evidence[5]—and FDA's application of this standard. In its recent draft guidance on the substantial evidence standard, FDA noted that various factors that can inform whether a sponsor should conduct one or two adequate and well-controlled clinical investigations.[6] These factors include a study's design, unmet medical need for a particular disease or condition, and feasibility and ethical considerations. Through this application of the substantial evidence standard, the Agency has struck a balance between, on the one hand, the importance of collecting clinical trial data that can "fairly and responsibly" be relied upon to conclude a drug is effective[7] and, on the other hand, concerns raised by strict adherence to a specific number of clinical trials.

BIO encourages the Agency to clarify that a requirement for more than two pain populations to support a general acute pain indication will either be redundant with one of the two pain models studies or would bring in a new model of pain (e.g., visceral) that should have its own indication. Assuming there is clear rationale for the drug and good grounding in biology, BIO recommends that the Agency consider that any non-opioid for acute pain, whether a novel MoA or not, should be held to the same evidentiary standard of two studies.

Use of FDA Expedited Programs

BIO appreciates the Agency's inclusion of policy regarding the application of expedited programs to non-opioid analgesic drug development. BIO recommends that FDA evaluate ways to increase the use of expedited programs, including Expedited Review which is defined in the PDUFA VII Commitment Letter, to non-opioid analgesics for acute and/or chronic pain.

FDA-Sponsor Engagement

BIO encourages the FDA, specifically the review division, to recognize and embrace its role in promoting efficient and effective drug development. Often during drug development, sponsors have experienced delays in meeting with the Division of Anesthesiology, Addiction Medicine and Pain (DAAP). BIO respectfully requests that CDER leadership provide additional oversight and guidance to the Division on expectations regarding timely and productive engagement with sponsors during development. The issue of promoting effective drug development was the subject of an FDA workshop in 2019[8], and the learnings from that workshop are relevant here. BIO's concern regarding the state of FDA's policy for development of drugs for pain and the status of the division's engagement with sponsors and the broader stakeholder ecosystem is best captured in remarks by Peter Pitts[9]:

> "*What senior agency management says publicly about the value and urgency of regulatory innovation has yet to permeate through its review divisions. This disconnect is causing a lack of faith within the broader healthcare ecosystem that FDA can be a potent ally in advancing patient access to new and important medical technologies. That is not a good thing. Faith must be restored and reinforced. […] Accepting change is difficult. More difficult for some than for others. And this means nothing less than accelerating an OND-wide review of the current and dangerous status of the regulatory status quo. The*

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[5] FDCA § 505(d).

[6] FDA, *Draft Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (Dec. 2019).

[7] *See* FDCA § 505(d).

[8] https://www.fda.gov/media/132221/download

[9] https://www.fda.gov/media/136577/download

most potent way that FDA can enable innovation is by being a partner in advancing new approaches to both drug development and regulatory science. And this begins at the conceptual policy level. Regulatory ambiguity does not instill confidence in an already high-risk development environment."

In the same workshop, BIO notes comments from then-Director Sharon Hertz, since retired, on a couple of key issues. First, Dr. Hertz questioned how more informal interactions between sponsors and the review division could work. Specifically, Dr. Hertz questioned the ability of the review division to engage in the practice of a sponsor reaching out to the review division by phone to get clarification of a key issue. This is a long-standing point of inconsistency across review divisions at FDA with some divisions being willing and flexible about getting on the phone with sponsors to clarify issues and provide timely guidance and others rigidly adhering to formal, usually written, communications. BIO supports the response from Peter Pitts advocating for more avenues for interaction between a sponsor and FDA in circumstances where "programs are being held up, if decisions are being held up on the sponsor level because of a lack of a that-sounds-right or that-doesn't-sound-right from the appropriate person within the appropriate division." Pitts' response makes an important point – a sponsor's decision on how to proceed with a development program may be delayed or even held up entirely due to lack of directional guidance from FDA. Overcoming this challenge requires two things:

1) More timely and flexible mechanisms for sponsors to engage with the right people in the review division to get clarity on the path forward; and
2) A culture within the review division that encourages thought-leadership and collaboration with sponsors to advise on complex or nuanced issues that may not be addressed or discussed in sufficient detail in formal policy.

And, as noted previously, a lack of formal guidance from FDA (as was the case for many years for acute pain and continues to be the case for chronic pain) exacerbates the challenges above and makes those less formal interactions and the engagement from reviews even more important for the field to move forward.

As shared with the Agency previously, BIO believes it is important for the review division and leadership to communicate both what is recommended or required to be done in a drug development program for pain and what is not recommended or unlikely to be successful. FDA reviewers are in the unique position of seeing various drug development strategies across molecules and over time, therefore having a valuable perspective on what may be successful and what is likely to be unsuccessful based on past experience. BIO believes it is possible and important, while protecting sponsors' commercial, confidential information, for FDA to share, ideally via inclusion in formal policy and guidance for industry, recommendations of what drug developers should avoid or approach with adequate mitigation strategies in their approaches to drug development. By looking across programs and reflecting on experience over time, BIO believes that inclusion of what not to do in drug development in formal Agency policy would greatly enhance the effectiveness and efficiency of the drug development process. Most importantly, this practice would improve the likelihood that the patients who participate in clinical research would be contributing to programs optimally designed to yield interpretable and high-quality results.

Chronic Pain Guidance Development

BIO urges the Agency to expedite efforts to publish policy on development of non-opioid analgesics for chronic pain. The gap in policy has resulted in development uncertainty, delays

and discontinuations, and BIO asks that the Agency act with urgency to address this issue and restore confidence in the field with regard to a viable regulatory pathway for development of non-opioid analgesics. In the same vein, we urge the Agency to act swiftly to revise the acute pain draft guidance to better reflect an intent to foster drug development of non-addictive alternatives to opioids.

Future Considerations and Next Steps

The challenges for development of non-opioid analgesics is two-fold with the release of the acute pain guidance:

1) the guidance appears to depart from the status quo to a higher bar and
2) intensifies the uncertainty regarding FDA's expectations for development of treatments for chronic pain.

Coupled with the challenges BIO's member companies experience in communications with the review division, including use of written response only and delays in meetings, BIO is concerned about the ability of the FDA to accomplish its goal of promoting development of non-opioid analgesics for treatment of pain. BIO proposes the Agency take a multi-pronged approach to improving the drug development landscape for non-opioid analgesics for pain:

1) Prioritizing the analysis of stakeholder comments on the acute pain guidance and communicating, with urgency and clarity, changes in policy to the public and to sponsors with active INDs;
2) Establishing a rapid and robust process for communicating the Agency's policy on development of non-opioid analgesics for chronic pain;
3) Translating the patient-focused drug development meetings on chronic pain and neuropathic pain to actionable insights for sponsors to leverage to advance drug development;
4) Identifying more nimble and timely ways to communicate the Agency's current policy on development of non-opioid analgesics for pain to support continuous improvement in the effectiveness of drug development in this space;
5) Evaluating the need for training or allocation of resources to support the review division in meeting PDUFA performance goals;
6) Establishing expectations for the review division's use of expedited programs, including Expedited Review as defined in the PDUFA VII Commitment Letter;
7) Hosting and engaging in scientific workshops to advance the Agency's understand and input into research efforts and priorities that have the potential to accelerate or improve the development of treatments for pain.

Sincerely,

/s/
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