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Modernizing the Pathway for Non-Opioid Analgesics

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On September 11, 2025, the US Food and Drug Administration (FDA) issued its draft guidance, Development of Non-Opioid Analgesics for Chronic Pain, opening a 60-day public comment period that will close on November 10 before the agency finalizes the document (FDA, 2025a). The draft marks a shift from the historical trial-and-error methods of chronic pain drug development toward a more rational and efficient model, an important step in a field defined by a high disease burden and an ongoing public health crisis where therapeutic progress has long lagged behind need (The Lancet Regional Health – Americas, 2023).

This document emerges from more than a decade of policy evolution. An earlier all-in-one analgesic draft proved unwieldy; it was later withdrawn and replaced by targeted guidance shaped by the SUPPORT Act's mandate—a 2018 law aimed at combating the opioid crisis—to foster non-opioid therapies. The FDA's focused documents on acute pain in 2022 and prolonged-duration local anesthetics in 2023 now culminate in this 2025 draft dedicated to chronic pain (FDA, n.d.-a; FDA, n.d.-b; Draft Guidance for Industry on Analgesic Indications, 2014; FDA, 2025b). Together, these efforts reflect a shift from primarily managing opioid risks toward actively enabling alternatives that could reduce opioid dependence.

The 2025 draft re-architects therapeutic agent development, establishing that a careful consideration of pain pathophysiology, paired with a drug's mechanism of action and tested in well-designed trials, enhances the likelihood of success. It grounds indication strategy in pathophysiology, allowing sponsors to pursue condition-specific, group-specific, or general chronic pain claims, with the breadth of the labeling tied explicitly to evidence that the drug's mechanism engages shared pathways across the targeted conditions.

Condition-specific indications address single pain disorders such as painful diabetic peripheral neuropathy, while group-specific claims encompass multiple conditions within a proposed group that share pathophysiology. General chronic pain indications span all pain types regardless of etiology. Substantiating evidence of effectiveness, which typically requires two adequate and well-controlled trials, may be reduced to one adequate and well-controlled trial plus confirmatory evidence when shared pathophysiology is scientifically justified. Broader claims demand compelling proof that the drug's mechanism engages pathophysiology common across all claimed conditions, with evidence requirements escalating accordingly.

On trial design, the guidance refines expectations while maintaining established standards and encouraging innovation. Randomized, double-blind, parallel-group superiority trials with 12-week treatment periods remain recommended, though shorter durations may be acceptable when discontinuation risks could impair interpretability. Placebo-controlled designs are preferred for safety assessment, while active-comparator noninferiority trials are discouraged due to trial-to-trial variability. Innovative adaptive designs, master protocols, Bayesian methods, real-world evidence, and digital health technologies are encouraged to improve efficiency. A further advance is the emphasis on patient-centric outcomes.

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Beyond pain intensity, functional outcomes such as activity level, sleep quality, and activities of daily living are highlighted as key outcomes. With respect to statistical rigor, the guidance also underscores transparent reporting and careful handling of missing data, explicitly discouraging single-imputation methods.

A key tension the draft acknowledges involves the interpretation of negative or inconsistent trial results. When an investigational drug fails in one chronic pain condition but succeeds in another, it remains uncertain whether the trial reflects a poor design, poor patient selection, or a distinct pain pathophysiology. Without deeper mechanistic work or biomarkers, we risk either discarding useful therapies or overgeneralizing from one pain condition to another. The document references HIV-related neuropathy trials as an example to illustrate this dilemma: an agent effective in diabetic and postherpetic neuropathies but failed to show benefit in HIV-associated cases, likely due to differing neural and immune pathophysiology rather than study error. This example illustrates that even clinically similar chronic pain syndromes can differ profoundly at a biological level. In the absence of objective mechanistic markers or stratification tools, such distinctions remain obscured, sustaining inefficiencies the FDA seeks to address.

Emerging evidence in pain neuroscience offers potential solutions. Baseline EEG rhythms, cortical connectivity, and functional MRI markers have shown unique responses to different analgesics, while measures of the endogenous pain modulatory system, such as conditioned pain modulation, have been shown to predict treatment sensitivity and risk for pain chronification. Integrating these biomarkers prospectively could enable mechanism-enriched trial designs where participants are grouped by underlying neurophysiologic profiles rather than broad clinical labels (Chaim et al., 2025; Jensen et al., 2014; Mackey et al., 2025; Melo et al., 2024). Placebo effects further complicate interpretation. Recent open-label studies demonstrate that placebo administration can meaningfully reduce pain and alter brain oscillations (Carvalho et al., 2021; Ortega-Márquez et al., 2025). These findings suggest that expectancy effects, compensatory pathways, and neural dynamics remain incompletely understood yet highly relevant to trial outcomes. Without directly engaging these foundational issues, the draft leaves certain conceptual gaps unaddressed. Its clear guidance on trial design and progressive endpoints is necessary but remains insufficient without parallel progress in pain neuroscience to support them.

The draft addresses public health priorities related to the opioid crisis by defining three opioid-related outcomes—avoidance, reduction, and elimination of opioid use—as clinically meaningful benefits that can be demonstrated in chronic pain trials and included in labeling. Avoidance is defined as preventing opioid initiation in opioid-naïve patients, reduction involves achieving clinically meaningful decreases in stable opioid doses, and elimination requires complete opioid discontinuation—all while maintaining comparable or superior pain control. The guidance emphasizes that these outcomes are public health goals and notes that programs incorporating them may, when appropriate, qualify for the FDA's expedited regulatory pathways.

The 2025 draft's strengths are evident: it clarifies indication architecture, reiterates core trial design expectations while encouraging innovative approaches, and explicitly connects efficacy to opioid-sparing outcomes. Its most forward-looking feature, tying broader claims to shared biology, will demand scientific progress to define and validate common mechanisms across conditions. While the document underscores the importance of biology, it provides limited clarity on how mechanistic evidence should function as confirmatory support when a single pivotal trial is proposed. As the FDA finalizes the document, greater clarity on confirmatory evidence criteria and practical strategies to address placebo response and intercurrent clinical events would enhance transparency and implementation.

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Conflicts of Interest

The authors declare no conflict of interest.

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