Development of Non-Opioid Analgesics for Chronic Pain

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2025
Clinical/Medical

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Development of Non-Opioid Analgesics for Chronic Pain Guidance for Industry[1]

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I. INTRODUCTION

FDA is committed to using its authorities to combat the opioid crisis. This guidance is intended to address two Agency priorities: (1) fostering the development of novel analgesic products and (2) decreasing opioid analgesic exposure and preventing new addiction.[2]

This guidance also responds to the statutory requirements of section 3001(b) of the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities (SUPPORT) Act, which directs FDA to issue or update existing guidance to help address challenges to developing non-opioid medical products to treat pain. In keeping with the mandate of section 3001(b) of the SUPPORT Act, and considering the severity of the ongoing opioid crisis, this guidance is intended to assist sponsors in the development of non-opioid analgesics for the treatment of chronic pain. It describes FDA's current recommendations regarding phase 3 trials for prescription non-opioid analgesic products being developed to treat chronic pain. It does not provide general recommendations on early phases of non-opioid analgesic drug[3] development. Nevertheless, early phases of non-opioid analgesic drug development are crucial, such as exploration of a drug's time to onset of analgesia, dose response, initial assessment of responses in relevant types of pain, preliminary assessment of durability of effect, and initial evaluation of drug safety. As with other drugs, non-opioid

[1] This guidance has been prepared by the Division of Anesthesiology, Addiction Medicine, and Pain Medicine in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] FDA's four priorities are decreasing exposure and preventing new addiction, supporting the treatment of those with opioid use disorder, fostering the development of novel pain treatment therapies, and improving enforcement and assessing benefit-risk. See the Opioid Policy Steering Committee web page, available at https://www.fda.gov/about-fda/office-medical-products-and-tobacco/opioid-policy-steering-committee.

[3] For the purposes of this guidance, all references to *drugs* include both drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) and therapeutic biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).

analgesics should have undergone sufficient development before their evaluation in phase 3 trials.

This guidance also does not provide specific recommendations on pediatric drug development. Sponsors are encouraged to begin discussions with the Agency about their pediatric clinical development plan early in their drug development program. For further information about required pediatric studies, FDA recommends sponsors refer to the draft guidances for industry *Pediatric Drug Development: Regulatory Considerations — Complying With the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act* (May 2023) and *Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations* (May 2023).[4]

This guidance does not address the development of drugs for the treatment of acute pain, which is the subject of a separate guidance;[5] local anesthetic drug products with prolonged duration of effect, which is also the subject of a separate guidance;[6] or opioid or opioid-containing analgesic products (henceforth referred to as *opioids* in this guidance).

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

Chronic pain is a leading cause of disability in the United States and worldwide and can be defined as pain that persists longer than 3 months. It may be attributed to various causes, such as a specific tissue injury (e.g., nerve injury), a primary manifestation of a disease (e.g., fibromyalgia), or one of many symptoms of a disease (e.g., cancer-related pain), or it may be idiopathic. Non-opioid analgesics approved for the treatment of some forms of chronic pain include serotonin and norepinephrine reuptake inhibitors, gabapentinoids (e.g., gabapentin and pregabalin), topical anesthetics (e.g., lidocaine patch 5%), and nonsteroidal anti-inflammatory drugs. Despite the availability of these treatments, a substantial proportion of patients with chronic pain have pain that is inadequately treated with non-opioid analgesics, with some

[4] When final, these guidances will represent FDA's current thinking on these topics. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[5] See the draft guidance for industry *Development of Non-Opioid Analgesics for Acute Pain* (February 2022). When final, this guidance will represent FDA's current thinking on this topic.

[6] See the draft guidance for industry *Development of Local Anesthetic Drug Products With Prolonged Duration of Effect* (March 2023). When final, this guidance will represent FDA's current thinking on this topic.

requiring initiation of opioids.[7] Because of the risks of abuse,[8] misuse, addiction, overdose, and death with opioids, facilitating development of non-opioid analgesics can help address the need for more analgesic treatment options and might reduce the need for opioid analgesics, important steps toward combating the opioid crisis.

Drug development programs for the treatment of chronic pain have historically been challenging, with many failures due to inability to translate promising nonclinical results into drugs with demonstrated clinical effectiveness with acceptable safety profiles. These challenges may be attributable in part to the clinical heterogeneity of patients with chronic pain and of chronic pain conditions, as well as our incomplete understanding of the mechanistic underpinnings of pain and analgesia. Advancing and incorporating mechanism-based knowledge of chronic pain conditions to the analgesic drug development process will be critical to address these challenges and would facilitate greater flexibility and efficiency in the drug development process. Accordingly, FDA is interested in the evolving research in pain mechanisms, particularly as they relate to identification of novel therapeutic targets, novel biomarkers, and patient phenotyping.

Although chronic pain remains insufficiently understood, it is recognized that there are shared mechanisms that are present in all chronic pain conditions as well as distinct mechanisms that may be seen in an individual chronic pain condition or a group of chronic pain conditions. Mechanistic descriptors and mechanism-based classification systems can be used to characterize the predominant pathophysiological pathways and resultant clinical manifestations of a given pain condition. Chronic pain has traditionally been categorized using two mechanistic descriptors: *nociceptive* or *neuropathic*. *Nociceptive* describes pain resulting from activation of nociceptors, the sensory receptors that transduce and encode noxious stimuli in response to actual or potential nonneural tissue damage. This pain type can be further divided into subtypes of *visceral pain* (e.g., pain attributable to pancreatitis or renal colic) or *somatic pain* (e.g., pain of osteoarthritis, low back pain, bone fracture, bone metastases, burns). *Neuropathic* describes pain caused by a lesion in or disease of the somatosensory nervous system. Based on the presumed location of the underlying lesion or dysfunction, this pain type may be further classified as *peripheral neuropathic pain* (e.g., painful diabetic peripheral neuropathy (pDPN), postherpetic neuralgia (PHN), complex regional pain syndrome (CRPS) type 2 (with nerve injury), HIV-

[7] Treede R-D, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA, Kaasa S, Korwisi B, Kosek E, Lavand'homme P, Nicholas M, Perrot S, Scholz J, Schug S, Smith BH, Svensson P, Vlaeyen JWS, and Wang SJ, 2019, Chronic Pain as a Symptom or a Disease: The IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11), Pain, 160(1):19–27; Cohen SP, Vase L, Hooten WM, 2021, Chronic Pain: An Update on Burden, Best Practices, and New Advances, Lancet, 397(10289):2082–2097; U.S. Department of Health and Human Services, 2019, Pain Management Best Practices Inter-Agency Task Force Report: Updates, Gaps, Inconsistencies, and Recommendations, available at https://www.hhs.gov/sites/default/files/pmtf-final-report-2019-05-23.pdf; National Institutes of Health, 2017, Federal Pain Research Strategy, available at https://www.ninds.nih.gov/sites/default/files/documents/FPRS_Research_Recommendations_Final_508C.pdf.

[8] As used in this guidance, the term *abuse* refers to the intentional, nontherapeutic use of a drug for its desirable psychological or physiological effects. The term *abuse* is used in this document to describe a specific behavior that confers a risk of adverse health outcomes. FDA is committed to reducing stigma, expanding therapeutic options, and ensuring access to evidence-based treatment for individuals with substance use disorders.

associated neuropathy) or *central neuropathic pain* (e.g., pain of spinal cord injury, post-stroke pain, pain associated with multiple sclerosis).

In 2016, the term *nociplastic* was introduced as a third mechanistic descriptor to describe pain that arises from altered nociception without objective evidence of actual or threatened nerve or tissue damage.[9] Nociplastic pain is generally considered to be a consequence of dysfunctional peripheral and central pain-processing pathways, manifesting as heightened sensitivity. Examples include fibromyalgia and CRPS type 1 (without nerve injury). Importantly, many chronic pain conditions can be described as an overlap of two or more mechanistic pain categories (e.g., some types of cancer pain, chronic low back pain, chronic post-surgical pain), so they may be considered as having a *mixed* pain origin.

The mechanistic descriptors and the pathophysiological mechanisms that they signify are important considerations in chronic pain classification systems. Contemporary systems such as the International Association for the Study of Pain (IASP) classification of chronic pain for the International Classification of Diseases (ICD-11),[10] the International Classification of Headache Disorders (ICHD-3),[11] and the ACTTION-American Pain Society Pain Taxonomy (AAPT)[12] incorporate prevailing understanding of pain mechanisms to indicate similarity (or dissimilarity) among pain conditions. These mechanism-based classification systems are intended to be dynamic and flexible, allowing the categorization of pain conditions to be aligned with prevailing thinking about pain mechanisms.

Incorporating mechanistic understanding in drug development is a rational approach that aligns with mechanism-based drug discovery and validation, mechanism-based diagnosis, and mechanism-based treatment plans. Careful consideration of both pain pathophysiology and the candidate drug's mechanism of action can inform the selection of a drug to target a particular pain condition(s), thus increasing the likelihood of a robust, successful clinical trial. Furthermore, mechanistic knowledge may support development for broader indications for a novel analgesic, beyond treatment of a single pain condition. Strong scientific justification, including compelling evidence of shared pain pathophysiology and demonstration that the drug targets that shared pathophysiology, may allow evidence of analgesic effectiveness to be

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[9] Kosek E, Cohen M, Baron R, Gebhart GF, Mico J-A, Rice ASC, Rief W, and Sluka AK, 2016, Do We Need a Third Mechanistic Descriptor for Chronic Pain States? Pain, 157(7):1382–1386.

[10] Treede R-D, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA, Kaasa S, Korwisi B, Kosek E, Lavand'homme P, Nicholas M, Perrot S, Scholz J, Schug S, Smith BH, Svensson P, Vlaeyen JWS, and Wang SJ, 2019, Chronic Pain as a Symptom or a Disease: The IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11), Pain, 160(1):19–27.

[11] Headache Classification Committee of the International Headache Society (IHS), 2018, The International Classification of Headache Disorders, 3rd edition, Cephalalgia, 38(1):1–211.

[12] Fillingim RB, Bruehl S, Dworkin RH, Dworkin SF, Loeser JD, Turk DC, Widerstrom-Noga E, Arnold L, Bennett R, Edwards RR, Freeman R, Gewandter J, Hertz S, Hochberg M, Krane E, Mantyh PW, Markman J, Neogi T, Ohrbach R, Paice JA, Porreca F, Rappaport BA, Smith SM, Smith TJ, Sullivan MD, Verne GN, Wasan AD, and Wesselmann U, 2014, The ACTTION-American Pain Society Pain Taxonomy (AAPT): An Evidence-Based and Multidimensional Approach to Classifying Chronic Pain Conditions, J Pain, 15(3):241–249.

generalized from related pain conditions to support indications for additional chronic pain conditions, or may be used as confirmatory evidence of effectiveness to support approval in a separate, closely related pain condition. In both cases, mechanistic knowledge is used to increase the efficiency of drug development and expand a drug's potential utility from one pain condition to multiple pain conditions.

It is important to recognize that our current understanding of pain pathophysiology and analgesic mechanisms of action is incomplete, thus limiting the ability to leverage information across chronic pain conditions in a simple, formulaic fashion. Although pain classification systems are based on data suggesting similar pain pathophysiology across conditions within a particular pain category, these systems alone may not provide sufficient justification for the use of mechanistic data as confirmatory evidence of effectiveness, as in the case of mixed pain conditions (e.g., chronic low back pain, chronic post-surgical pain) or for drugs that act on pathophysiology present in multiple pain categories (e.g., central sensitization, inflammation).

Furthermore, based on existing knowledge, even within well-defined mechanistic categories, such systems have not been sufficiently reliable to predict the analgesic response to a drug across all conditions within a category. This may, in part, relate to the common occurrence of mixed pain mechanisms, even for conditions within a category, or to differences in susceptibility to a drug's specific mechanism(s) of action for conditions within a category. For example, there have been failed clinical trials in HIV-related painful sensory neuropathy with several drugs that had already been FDA-approved for the treatment of other painful peripheral neuropathies (e.g., pDPN and PHN). Although it is unclear whether these unsuccessful trials were due to study design or unknown pain mechanisms unique to HIV-related painful sensory neuropathy, the results suggest that treatment effects from one pain condition may not predict response of a drug to another pain condition in the same category.

Despite these limitations, current knowledge regarding pain pathophysiology does allow for the possibility of using efficacy data from one pain condition to support an indication in another with adequate scientific justification, as will be discussed in the following sections. Existing knowledge of individual chronic pain conditions can be augmented with evidence that includes shared pain pathophysiological mechanisms, other shared characteristics,[13] and drug pharmacodynamics relevant to those shared mechanisms, as well as new scientific knowledge about pain mechanisms or analgesic pathways. It is anticipated that the ability to identify shared pathophysiology, and to leverage information and/or reliably generalize analgesic effectiveness across pain conditions, will improve as scientific knowledge accumulates. Thus, a key priority for analgesic drug development is the advancement of mechanistic knowledge to gain deeper understanding of pain pathophysiology and introduce innovative drugs that target novel analgesic pathways.

[13] There may be other pain characteristics that are shared between conditions (e.g., clinical presentation, mechanisms of injury, anatomic locations, and/or drug effect targets) and that are targeted by the analgesic's mechanism of action. Sponsors would need to provide evidence for the characteristics that are shared among pain conditions and evidence that the proposed analgesic's mechanism of action targets the shared characteristics.

Building an evidence-based, mechanism-based framework for analgesic drug development will help the field move away from historical trial-and-error methods toward more rational, efficient approaches that will support the approval of safe and effective non-opioid analgesics. Acknowledging that there will be new insights in pain research in the future, the general drug development approach discussed below is intended to be adaptable based on the best available evidence at the time.

III. DEVELOPMENT PROGRAMS FOR NON-OPIOID ANALGESICS FOR CHRONIC PAIN

A. Establishing Indications for Non-Opioid Analgesics for Chronic Pain

1. General Considerations

For the purposes of this guidance, chronic pain indications can be described as targeting specific chronic pain conditions (i.e., *condition-specific*), a group of chronic pain conditions (i.e., *group-specific*), or all chronic pain (i.e., *general chronic pain*). These indication types are further described in the sections below. Note that the particular language of the labeled indication will be based on the data. Sponsors are encouraged to discuss the indications being sought with FDA as early as feasible.

Historically, sponsors have sought indications targeting specific chronic pain conditions, both for initial and subsequent approvals. However, it may be possible to seek a broader group-specific or general chronic pain indication. It is reasonable to expect that a drug development program would build upon approvals for specific pain conditions before seeking approval of a broader pain group. Similarly, it would be reasonable to expect that a program would build upon approvals of pain conditions and/or pain groups before seeking an approval targeting all chronic pain.

Generally, at least two adequate and well-controlled trials are necessary to provide substantial evidence of effectiveness.[14] In certain circumstances, it may be possible to decrease the number of trials required (i.e., increase the efficiency of an analgesic development program) through the use of a single adequate and well-controlled trial plus confirmatory evidence of effectiveness (e.g., based upon a positive trial in a related condition), as discussed in more detail in section III.A.2. Generalizing analgesic effectiveness across pain conditions may also be possible and is discussed in section III.A.3. Both the use of confirmatory evidence and the generalization of effectiveness require strong scientific justification through evidence that the conditions have shared pain pathophysiology and the drug's mechanism of action is both clearly understood and shown to directly target the major driver or drivers of the shared pain pathophysiology. Thus, to increase the efficiency of an analgesic development program as described above, sponsors should provide the scientific basis to support that the pain conditions being evaluated have

[14] Section 505(d) of the FD&C Act (21 U.S.C. 355(d)); see draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent FDA's current thinking on this topic.

shared pathophysiology and that the drug's mechanism of action targets this shared pathophysiology. This evidence is critical for supporting use of confirmatory evidence and generalization of effectiveness. As previously mentioned, in some cases, it may be possible to leverage current pain classifications (e.g., AAPT, ICD-11) and their underlying evidence as scientific justification for the shared pathophysiology. However, if the drug cannot be demonstrated to target that shared pathophysiology, use of confirmatory evidence or generalization of analgesic effectiveness may not be appropriate, as discussed further below. FDA is receptive to proposals for efficient and streamlined development programs, as discussed below and further described in section III.B.5, Innovative Approaches.

In addition to providing substantial evidence of effectiveness, a clinical development program must also establish the safety of the product for its intended use, including a thorough assessment of abuse and misuse potential; that is, the program must demonstrate that the benefits of the drug outweigh its risks under the conditions prescribed, recommended, or suggested in the proposed labeling.[15] The acceptability of the risks may depend on factors such as the drug's effectiveness, the nature of the condition being treated, and the availability of alternative treatments.[16]

2. Condition-Specific Indication

Traditionally, non-opioid analgesics for chronic pain have been indicated for one or more specific pain conditions (i.e., a condition-specific indication). *Treatment of neuropathic pain associated with pDPN* is an example of a condition-specific indication.

There are several approaches for obtaining an indication for a specific pain condition. As stated above, generally, at least two adequate and well-controlled trials are necessary to provide substantial evidence of effectiveness (e.g., two trials in pDPN for an indication in pDPN). However, as described above in section III.A.1, under certain circumstances it may be appropriate to obtain a condition-specific indication based on one adequate and well-controlled trial plus evidence of effectiveness in a closely related pain indication, serving as confirmatory evidence of effectiveness (see examples below).[17] This requires scientific justification through evidence that the two indications have shared pain pathophysiology and that the drug's mechanism of action directly targets the shared pathophysiology.

The following examples demonstrate how confirmatory evidence of effectiveness might be used in the development of non-opioid therapies for chronic pain. A sponsor provides scientific justification that two conditions, for example PHN and pDPN, have shared pain pathophysiology and that their drug's mechanism of action directly targets the shared pathophysiology. To add a new condition-specific indication for treatment of PHN to a drug already approved for pDPN,

[15] See section 505(d) of the FD&C Act (21 U.S.C. 355(d).

[16] For further information on this topic, see the guidance for industry *Benefit-Risk Assessment for New Drug and Biological Products* (October 2023).

[17] Section 505(d) of the FD&C Act (21 U.S.C. 355(d); see draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023). When final, this guidance will represent the FDA's current thinking on this topic.

the sponsor could submit data from a single adequate and well-controlled trial in PHN plus confirmatory evidence, as provided by results from the clinical trials that formed the basis of the previous approval in pDPN. If a sponsor wanted to obtain *concurrent* approval of a drug for pDPN and PHN, one adequate and well-controlled trial in each condition would be conducted, and each trial could be used as confirmatory evidence for the other indication, thereby supporting concurrent approval of the drug for two condition-specific indications. In this scenario, approval is contingent on a persuasive, positive adequate and well-controlled trial in each pain condition. Because each trial serves as the confirmatory evidence for the other proposed condition-specific indication, neither condition-specific indication would likely be approved if one of these trials is negative.

Sponsors intending to establish substantial evidence of effectiveness using one adequate and well-controlled clinical investigation plus confirmatory evidence should consult FDA in advance to discuss the appropriateness of such an approach for their development program.

3. Group-Specific Indication

A group-specific indication would reflect a conclusion that the drug acts on a mechanism that is shared across pain conditions within a sponsor's proposed group and is, therefore, effective for all conditions within the group. As stated previously, sponsors should provide the scientific basis to support that the pain conditions being evaluated as a group have shared pathophysiology and that the drug's mechanism of action targets this shared pathophysiology (see sections II, Background, and III.A, General Considerations). This requires that evidence of effectiveness be generalized from several specific pain conditions to a broader group of closely related pain conditions, potentially including conditions not studied in the drug's analgesic clinical development program. An indication for a broader set of pain conditions than those studied in controlled trials may, therefore, only be appropriate after careful consideration of the generalizability of the evidence, the consistencies in the disease process across different conditions within a group, the scientific evidence that the drug's mechanism will target a common underlying cause of pain across these conditions, the prevailing scientific knowledge, and the benefit-risk analysis across all specific conditions within the proposed broader indication.

The exact requirements for generalizing to a group-specific indication will depend upon a number of factors, as described in the paragraph above. Beyond the trials necessary to establish substantial evidence of effectiveness, there is no established number of trials or conditions necessary to obtain a group-specific pain indication, as the justification for broader indications depends heavily on the drug's intended target and mechanism of action and the robustness of data across several trials. It is expected that a development program seeking a group-specific pain indication will build upon condition-specific indications. Additional positive trials in different patient populations sharing the same pathophysiological mechanism (e.g., patients with other specific conditions not previously studied in the drug's development program, patients with conditions considered to be of mixed pain etiology, patients with different pain conditions in the proposed group) may provide support that the drug is effective for all chronic pain conditions in the proposed group.

Seeking a group-specific indication will require careful planning. Therefore, FDA encourages sponsors to engage with the Agency as early as feasible to obtain feedback specific to their drug development program.

4. General Chronic Pain Indication

The broadest indication, a general chronic pain indication, would reflect a conclusion that the product is effective for all chronic pain conditions. As with group-specific indications, a general chronic pain indication requires that analgesic effectiveness be generalized from single pain conditions to other pain conditions. However, unlike group-specific indications, where multiple lines of evidence must be evaluated to judge whether one pain condition belongs in the same group as another, a general chronic pain indication encompasses all chronic pain conditions. The mechanisms leading to the clinical manifestation of chronic pain *are* the shared pathophysiology. Therefore, a general chronic pain indication would require data adequate to support that the drug acts on pathophysiology present in all chronic pain types and that the drug is effective regardless of the underlying etiology of the chronic pain.

As with group-specific indications, there is no established number of trials or conditions necessary to obtain a general chronic pain indication, as the justification for broader indications depends heavily on the drug's intended target and mechanism of action and the robustness of data across several trials. It is expected that a development program seeking a general chronic pain indication will build upon condition-specific and/or group-specific indications. Positive trials with persuasive results in a range of different patient populations (e.g., patients with conditions considered to be of mixed pain etiology and patients with different specific pain conditions across different groups of pain conditions) may provide support that the drug is effective for all chronic pain conditions. In addition, results from acute pain trials may be considered to support the totality of the evidence in consideration of a broader indication. However, acute pain models do not always translate to chronic pain efficacy.

The clinical development programs for general chronic pain indications can be challenging. Seeking a general chronic pain indication requires careful planning with respect to the population enrolled, study design, and statistical analysis plans, so FDA encourages sponsors to engage with the Agency to obtain feedback specific to their drug development program. Additionally, sponsors should provide support for how the dosing regimen is expected to be efficacious across multiple chronic pain conditions with distinct etiologies.

B. Trial Design Considerations

Sponsors developing non-opioid analgesic products for chronic pain should consider the following recommendations as they design the clinical trials in their development program. Careful consideration of both pain pathophysiology and the candidate drug's mechanism of action can increase the likelihood of a robust, successful clinical trial.

1. General Trial Design

Sponsors pursuing an initial approval for a chronic pain indication should include (a) at least one randomized, controlled, double-blind, parallel-group superiority trial in their product's drug development program, along with (b) at least one additional randomized study (see *Additional Randomized Trial Designs* below). A randomized, controlled, double-blind, parallel-group superiority trial design provides valuable information on the treatment effect size and safety. The design and number of additional randomized trials would depend on the indication(s) sought. Example trial designs and characteristics are further described below.

Suitable comparators for chronic pain trials include a placebo, a lower dose of the same investigational drug that is anticipated to be less effective than the higher dose, or an active control (where the intention remains to demonstrate superiority of the study drug over the active control drug). Note that across all of these trial designs, the study drug is typically evaluated as add-on treatment to the participant's current stable analgesic pharmacological and non-pharmacological regimen. Superiority-designed trials comparing the study drug to an active control, or a lower dose of the study drug, may result in more limited safety information in contrast to placebo-controlled studies but may provide clinically useful comparative information on effectiveness and safety when an appropriately selected comparator agent is employed. If feasible, development programs should include placebo-controlled studies.

Active-comparator noninferiority trials are generally less reliable in chronic pain drug development programs and are therefore more challenging to use as effectiveness trials for analgesics. In a noninferiority trial, the objective is to demonstrate that the treatment effect of the study drug is not materially worse than that of the control to support a conclusion that the study drug is effective. A noninferiority study, absent a placebo control arm, requires confidence that the active control provides the expected extent of analgesic effect as seen in prior trials of the drug (supporting "assay sensitivity"). Trial-to-trial variability in analgesic efficacy is often observed, and occasionally trials may fail to demonstrate efficacy, such that the "constancy" assumption, essential for interpretation of noninferiority trials, may not be met. Because the analgesic effect of approved analgesics may not be replicated across clinical trials and across pain conditions, it may not be possible to predefine a reliable noninferiority margin. Consequently, a clinical trial that includes a concurrent placebo arm to demonstrate effectiveness of the active control is recommended.[18] Sponsors interested in conducting a noninferiority-designed study to demonstrate effectiveness should discuss this with FDA early in the drug development process.

The recommended duration of the double-blind treatment period is usually 12 weeks. However, this duration of the controlled treatment period may be difficult in trials evaluating participants with severe pain conditions because of the potential for a high rate of treatment discontinuations, for example, in the placebo arm because of inadequately controlled pain, even with the use of rescue therapy. The potential for an increased rate of discontinuation during a 12-week

[18] See the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

controlled period could impair interpretability of trial results, including the assessment of durability of treatment effect. Therefore, in some chronic pain conditions, and if scientifically justified, the duration of the controlled treatment period could be shorter, with the time point for primary efficacy evaluation selected at a point where the number of discontinuations is expected to be limited (see section III.B.4). In such situations, the additional randomized trial(s) in the development program could be used to demonstrate both drug effectiveness and durability, as discussed in the next paragraphs.

Additional Randomized Trial Designs

There are a number of possible study design options for the additional randomized trial(s) that can be considered. These can include an active-comparator study with a superiority design, a placebo-controlled study design evaluating proportion of participants able to achieve sustained pain control over a longer period of time (e.g., after 6 to 12 months) with secondary endpoints evaluating average daily pain, a placebo-controlled study of participants on opioid treatment for chronic pain evaluating reduction or elimination of opioids (see section III.D), or an enriched enrollment randomized withdrawal (EERW) trial design.[19] The latter design has potential advantages and a number of important limitations and is discussed further below. In addition, as noted in this section above, an active-comparator noninferiority study may be considered, but the limitations noted above would need to be addressed and early discussions with FDA held.

In an EERW trial, all study participants who meet screening eligibility criteria receive an open-label study drug in a pre-randomization run-in phase. Those participants who tolerate the drug and meet prespecified criteria for improvement in pain (i.e., the enriched population) are enrolled in a treatment phase where they continue to receive the open-label study drug for a defined duration of time. Participants who continue to have adequate pain control during the open-label treatment phase and tolerate the study drug then enter a double-blind study drug withdrawal phase where participants are randomized to either continue the study drug or switch to placebo (i.e., withdrawal of active therapy). Depending on the characteristics of the study drug, study drug withdrawal may need to be conducted on a tapering schedule. Effectiveness is assessed at the end of the randomized withdrawal period. Based on the length of the open-label treatment period before the withdrawal period, durability of effectiveness beyond 12 weeks can also be evaluated. The details of study design will be determined based on the facts and circumstances of each particular drug and development program.

A strength of the EERW design is that it can support drug effectiveness by demonstrating a between-group difference on the effectiveness endpoint (e.g., pain intensity or time to failure) after the randomized withdrawal of the active drug, as well as showing durability of response (treatment period with the test agent pre-randomization and during the randomized withdrawal period). However, the estimate of effectiveness is only in a selected population, namely, participants who appear to respond to and are tolerating the drug; the design does not provide an estimate of the treatment effect size or the proportion of responders in the overall population. Another limitation is that if the drug has central nervous system effects, participants may

[19] See the guidance for industry *Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products* (March 2019).

experience drug withdrawal or otherwise note a change in sensorium, which could result in unblinding of the participant and investigator, thus confounding a robust assessment of drug effectiveness. Gradual down-titration after randomization into the withdrawal period may be able to mitigate this concern.

Additionally, the EERW design does not provide a robust evaluation of the drug's safety profile; safety information from the open-label period is uncontrolled, and only participants who tolerate the drug enter the randomized treatment period, limiting the value of the safety observations from this period. As a result, the primary source of safety assessment for the drug product is the randomized-comparator superiority studies discussed earlier. The acceptability of EERW-designed trials in a development program will depend on the ability to address and mitigate the issues with this design and the extent of efficacy and safety data from other controlled trial designs in the program. Sponsors are encouraged to discuss the details of their protocol with FDA.

For sponsors interested in incorporating assessments of opioid use (i.e., avoidance, elimination, or reduction) into their development program, such a study may also be able to contribute to the assessment of effectiveness and durability of the treatment effect (see section D below).

2. Trial Population

Sponsors should carefully consider a trial's eligibility criteria to ensure that the enrolled population is relevant to the target patient population. Sponsors should leverage established diagnostic criteria, when available, to identify participants with the chronic pain condition of interest (e.g., American College of Rheumatology criteria for fibromyalgia, osteoarthritis of the hip, and osteoarthritis of the knee). When such diagnostic criteria do not exist, sponsors should provide scientific justification for the enrollment criteria defining the study population. Additionally, the enrollment criteria should select participants with pain of appropriate intensity and chronicity (e.g., at least 3 months) to minimize the potential impact of factors such as the spontaneous resolution of pain or excessive fluctuation in pain, which may complicate the detection of a treatment effect.

Sponsors can consider incorporating an extended screening or preenrollment phase to evaluate participants' baseline pain severity and allow exclusion of participants with milder pain or with a high extent of variability in pain intensity. This preenrollment phase may also be used to identify participants who can comply with recording their pain scores. Sponsors should avoid overly restrictive enrollment criteria, where possible, to maximize the generalizability of the results. For example, geriatric participants or participants with renal or hepatic disease should not be routinely excluded from trials in the absence of a potential safety concern.

Sponsors should enroll participants who reflect the characteristics of clinically relevant populations, including considerations for sex, race, and ethnicity.[20]

3. Background Therapy and Rescue Medication

Sponsors may choose to enroll participants who are on background therapies for chronic pain. These may include both non-pharmacological (e.g., ice, heat, physical therapy, acupuncture, psychological support, procedural interventions, neuromodulation) and pharmacological treatments. Protocols should prespecify the allowed background therapies. All background therapies should ideally be maintained at stable doses (or intensity, for non-pharmacological treatments) and for a protocol-specified, minimum duration before study enrollment and should be carefully documented. Patients experiencing continued pain at a protocol-required pain intensity, while on background therapies, would be eligible to enter the study.

Rescue medication is a critical design feature of chronic pain trials given the importance of ensuring adequate pain control in study participants, but it can pose problems in the evaluation of the study drug effect. Protocols should prespecify the allowed rescue medications, including the type, frequency, amount, and threshold of pain at which allowable rescue medications can be administered. The rescue medication chosen will depend on the pain condition being studied, would preferably be short-acting and of a pharmacological class that is different from the study drug, and should be expected to provide adequate analgesia so that a reasonable number of participants randomized to placebo can remain on this treatment arm, minimizing treatment discontinuation for lack of efficacy.

Rescue medication use should be well-documented to support the validity of the study, as the differential use of rescue medication between treatment arms can impact results in a variety of ways and decrease the apparent effect of the study drug. The approach to handling the use of rescue treatment in the statistical analysis is discussed below.

If rescue medication is needed, it would be important for participants to assess their pain and record their pain score before using the rescue medication. In circumstances where the pain is being assessed at a clinic visit, it may be appropriate to limit the use of rescue medication before collecting pain scores. For example, protocols assessing pain at clinic visits using standardized instruments (e.g., via the Western Ontario and McMaster Universities Osteoarthritis Index, also known as the WOMAC pain subscale) should, if clinically feasible, aim to reduce rescue medication use in the 24 hours before the clinic visit.

[20] See, for example, p. 15 of the ICH guidance for industry *E8(R1) General Considerations for Clinical Studies* (April 2022): "Studies conducted in the later phases of drug development or post-approval are often more heterogeneous in study population definitions. Such studies should involve participants who are representative of the diverse populations that will receive the intervention in clinical practice." See also, for example, 21 CFR 315.50(d)(5)(v) (requiring that effectiveness data in an NDA "must be presented by gender, age, and racial subgroups and must identify any modifications of dose or dose interval needed for specific subgroups").

4. Discontinuations

Appropriate assessment of both effectiveness and safety relies on the minimization of the occurrence of missing data and accurate and complete capture of the reason for participant discontinuation. Sponsors should ensure that when a participant discontinues the study treatment and/or withdraws from the trial that the specific reason is obtained. Sponsors should provide detailed information with specific causes, rather than report terms such as "other," "participant request," "investigator decision," or other such nonspecific categories. Sponsors also should ensure that case report forms are designed to accurately capture the reason(s) for participant treatment discontinuation and/or participant withdrawal from the trial. Furthermore, participants should generally be encouraged to stay in the study after treatment discontinuation through the end of the controlled period for collection of safety and efficacy data.

5. Innovative Approaches

FDA encourages proposals for efficient and streamlined development programs, including innovative approaches. Complex innovative trial designs (e.g., a mixture of elements such as adaptive design, master protocols, Bayesian methods) and model-informed drug development have the potential to improve trial efficiency. Use of real-world evidence (e.g., randomized trial with pragmatic elements) or decentralized trial elements could also be considered as innovative approaches to support approval of novel analgesics, either as part of an adequate and well-controlled trial or as confirmatory evidence of effectiveness. Furthermore, trial execution could be facilitated by the use of digital health technologies. As information about the underlying disease mechanisms associated with specific pain conditions increases, and as molecularly targeted drug treatments for pain are developed, the use of biomarkers to increase development efficiency should also be considered.[21]

These examples represent only a few of the many innovative approaches that may be applicable to the development of non-opioid analgesics for chronic pain. Sponsors considering any innovative approach are strongly encouraged to both review relevant FDA guidance and engage with the Agency early in development.[22]

[21] For example, biomarkers predictive of drug response (e.g., pharmacogenomic) could be used to enrich trials with potential responders, allowing for smaller studies to demonstrate effectiveness.

[22] See the guidances for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* (December 2019), *Master Protocols for Drug and Biological Product Development* (December 2023), *Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products* (August 2023), *Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice* (September 2024), *Conducting Clinical Trials With Decentralized Elements* (September 2024), *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations* (December 2023), and *Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products* (December 2020).

C. Effectiveness Considerations

In chronic pain trials, the primary endpoint should generally be based on a well-defined and reliable patient-reported outcome measure of the participant's pain intensity ("pain intensity score").[23] Generally, a numerical rating scale is used (e.g., 11-point numerical rating scale). If available and adequately developed, disease-specific pain measures may be preferable to non-disease-specific measures, as they may be more sensitive to clinically meaningful change. In an EERW-designed trial, a numerical rating scale is generally the preferred approach; however, the use of a time-to-failure endpoint may be considered for the randomized withdrawal period with the pain scale as a key secondary endpoint (see discussion in section III.B.1 above).

The pain intensity score should be recorded daily at the same time each day. In addition, patients should be counseled at each visit to record pain intensity just before taking rescue medication, if rescue medication is needed. All rescue medication used should be recorded (including dose, date, and time administered), and sponsors should capture the reasons for rescue medication use (e.g., ineffective pain control of study condition, other pain unrelated to study condition, anxiolysis). Use of any non-pharmacological rescue interventions should also be captured. FDA recommends the use of electronic pain diaries, which allow time-stamped data to be electronically transferred to investigators and sponsors.

The primary endpoint in comparator-controlled (i.e., placebo or active comparator) superiority trials should be defined as the change in the average daily pain score (measured over 7 days) at the end of the treatment period compared with the average of the daily pain scores at baseline (measured over the 7 days before randomization). The use of a 7-day average pain score reduces the impact of daily variability, improving detection of a therapeutic effect of the study drug on pain intensity.

FDA recognizes the connection between pain and an individual's functional status and notes that improvement in functional outcome measures may be useful in informing the benefit-risk assessment. As such, FDA encourages sponsors to assess relevant functional measures (e.g., activity level, sleep quality, activities of daily living). Sponsors seeking such treatment benefit claims in addition to analgesia could prospectively identify change in functional status as a key secondary endpoint with appropriate control for type I error. When evaluating function, sponsors should use a disease-specific measure of function, when available, or a different well-defined and reliable measure.[24]

[23] This stands in contrast to pain relief scales, which require participants to report current pain relative to their prior pain experience and may be influenced by other factors including patients' ability to recall their prior experience of pain.

[24] Although this guidance discusses the selection of endpoints for clinical trials, it does not address detailed design considerations for patient-reported outcome instruments. See the FDA Patient-Focused Drug Development (PFDD) guidance series (available at https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical), which is part of FDA's PFDD efforts in accordance with the 21st Century Cures Act and the Food and Drug Administration Reauthorization Act of 2017, Title I.

Secondary outcome endpoints may further characterize the efficacy of an analgesic and support the primary efficacy endpoint. Depending on the indication, these could include the following:

- Proportion of participants with ≥30% pain reduction at the end of the treatment period
- Proportion of participants with ≥50% pain reduction at the end of treatment period
- The amount of rescue medication used
- A patient global impression of change in pain
- Change in score for fit-for-purpose,[25] disease-specific measures

In addition, FDA recommends the evaluation of cumulative responder curves[26] for change in the average daily pain score at the end of the treatment period as a supplementary analysis, and curves showing average pain over the entire treatment period.

D. Evaluating Avoidance, Elimination, or Reduction of Opioid Use

Given the risks of opioid use, decreasing opioid analgesic use while still maintaining pain control is an important public health goal. This section provides FDA's recommendations on the design of trials dedicated to the evaluation of opioid avoidance, elimination, or reduction in patients with chronic pain.[27]

For purposes of this guidance, the term *avoidance* refers to the ability of the non-opioid to adequately treat pain without the initiation of an opioid (i.e., avoid initiating use); *elimination* refers to the ability of the non-opioid to adequately treat pain by completely replacing opioid therapy (i.e., eliminate use); and *reduction* refers to the ability of the non-opioid to adequately treat pain with a lower amount of opioids (i.e., reduce dose or duration of use). If supported by clinical trial results, claims of opioid avoidance, elimination, or reduction would appear in the Clinical Studies section of product labeling.

Importantly, for pain conditions that are not typically responsive to opioids or for which opioids are not typically needed (e.g., fibromyalgia), the claims referenced above would generally not be considered appropriate.

Robust results from at least one adequate and well-controlled trial would be required to demonstrate a reduction in opioid use to support inclusion in the Clinical Studies section of labeling.[28] If appropriately designed, this trial can contribute to the evidence of analgesic

[25] See the draft guidance for industry, Food and Drug Administration staff, and other stakeholders *Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments* (June 2022). When final, this guidance will represent FDA's current thinking on this topic.

[26] Also referred to as empirical cumulative distribution function (eCDF) curves.

[27] Consistent with the feedback of the Anesthetic and Analgesic Drug Products Advisory Committee on November 15, 2018, FDA believes the term *opioid-sparing* as a statement in labeling is unlikely to be sufficiently descriptive to be meaningful. Instead, FDA recommends labeling that more clearly and specifically explains the benefits provided by avoiding, eliminating, or reducing opioid analgesics use, as discussed in section III.D of this guidance.

[28] See 21 CFR 201.57(c)(15).

effectiveness. FDA recognizes that sponsors may be interested in exploring the use of alternative study designs related to claims concerning opioid use and recommends they engage the Agency early in their planning.

The selection of the trial population will depend on the particular wording proposed for product labeling (e.g., avoidance, elimination, or reduction). For instance, to demonstrate avoidance of opioid initiation, a placebo-controlled study, as discussed in section III.B of this guidance, could be used. The trial could enroll opioid-naïve participants with poorly controlled pain for whom initiation of opioid therapy would usually be appropriate (i.e., would typically be the next step in the patient's pain management strategy). Participants would be randomized to either the study drug or placebo and permitted opioid rescue medication as needed for pain control. Demonstration of superiority in pain control of the study drug over placebo, while demonstrating via a secondary endpoint a statistically significant, clinically meaningful greater proportion of participants not requiring any use of opioid rescue medication (i.e., avoidance of initiation), could potentially support language regarding avoidance of opioid initiation.

To demonstrate a reduction in or elimination of opioid use, a trial could enroll participants whose pain is being treated with a stable, regular dose of opioids, who have not been successful in documented efforts to down-titrate or to discontinue opioid treatment, or who demonstrate a continued need for opioid therapy during the run-in period. These participants could be randomized to receive study drug or placebo added to their current opioid regimen. As these participants may be opioid-tolerant, they would undergo a carefully monitored down-titration of their current opioid regimen over a time period that minimizes the risk of abrupt opioid withdrawal while maintaining adequate pain control (i.e., pain intensity in the study drug plus opioid group must be comparable or superior to pain intensity in the placebo plus opioid group). Down-titration would occur over the randomized treatment period but may also occur during the run-in period (if down-titration is included in the protocol to ensure continued requirement for opioid to control the participant's pain). Opioid use–related endpoints could include the difference between treatment arms in the proportion of participants who met a prespecified, clinically meaningful threshold reduction in the amount of opioid medication use (i.e., reduction in opioid use), or the proportion of participants who were able to completely titrate off opioids by a prespecified, clinically meaningful time point through the end of the trial (i.e., elimination).

A statistically significant difference in opioid medication reduction or elimination would be needed if a claim is to be included in labeling. In the case of reduction, sponsors may also need to demonstrate a clinically meaningful benefit attributable to opioid use reduction (e.g., decrease in opioid-related adverse reactions). Opioid medication elimination itself is considered a clinically meaningful benefit. The specific study design and primary endpoints should be discussed with FDA.

FDA does not recommend use of electronic health care data (e.g., electronic health record or administrative claims data) to measure opioid use or support claims of clinically meaningful reductions in opioid use. These data sources can provide information on prescribing and dispensing patterns, but they are generally not sufficient for obtaining an accurate assessment of actual opioid use. If sponsors are considering the use of electronic health care data, discussions with the Agency are highly recommended.

However, electronic health care data may provide useful information when planning a clinical trial. For instance, such data may be valuable in understanding current practices and standards of pain management in specific patient populations and health care delivery settings and in identifying patients who may be eligible for trial participation. FDA remains interested in feedback on ways in which these data could be useful to support the approval of non-opioid analgesic products.

E. Safety Considerations

The size of the expected safety database, the duration of controlled safety data collection, and the specific types of safety data needed will be affected by whether the drug is a new molecular entity, its mechanism of action, class-specific concerns, and its intended duration of use. Additionally, nonclinical safety findings or safety signals identified during clinical development will also affect the extent of clinical exposure necessary in the safety evaluation. Altogether, these factors may necessitate a safety database that is larger and/or contains data from a longer exposure duration than that recommended in the ICH guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions* (March 1995).

Drugs that affect the central nervous system that are chemically or pharmacologically similar to other drugs with known abuse potential or that produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential; a proposal for scheduling under the Controlled Substances Act will be required at the time of the new drug application submission.[29] For information on the abuse potential evaluation and information required at the time of the new drug application submission, see the guidance for industry *Assessment of Abuse Potential of Drugs* (January 2017).

For reformulations of drugs with existing chronic indications, including chronic pain, the size of the safety database should reflect the differences from existing formulations of the drug and any gap in safety data expected from these differences. To determine an appropriate number of participants for the safety database for a drug previously approved for a non-analgesic indication, sponsors should consider the extent of differences between the previous patient population studied and the analgesic population under evaluation and whether the differences alter the risk for adverse reactions. Additional studies may be necessary based on the type of reformulation (e.g., a change from an oral to intravenous formulation). Selective safety data collection, as described in the ICH guidance for industry *E19 A Selective Approach to Safety Data Collection in Specific Late-Stage Pre-Approval or Post-Approval Clinical Trials* (December 2022), could also be considered for a drug with a well-understood safety profile.

Early in development, sponsors should discuss safety considerations, including the safety database requirements, with FDA.

[29] 21 CFR 314.50(d)(5)(vii).

F. Statistical Considerations

It is generally recommended that the primary efficacy analysis population include all randomized participants, consistent with the intent-to-treat principle.[30] In trials that are double-blinded, it may be reasonable to use all randomized participants who receive at least one dose of the treatment with justification included, known as the modified intent-to-treat population. Sponsors should prespecify the primary efficacy analysis population and designate the other population as the analysis population for supplemental analyses.

To improve the precision of treatment effect estimates, FDA recommends that analyses be adjusted for prespecified baseline covariates (e.g., baseline pain score, and in osteoarthritis participants, for example, index joint, Kellgren-Lawrence grade). For further information on covariate adjustment, see the guidance for industry *Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products* (May 2023).

Sponsors are encouraged to prespecify the estimand that is associated with the clinical question of primary interest and clearly specify how intercurrent events will be handled in the primary analysis. Intercurrent events may include, for example, discontinuation of assigned treatment or use of non-protocol-specified rescue medications while the trial is ongoing. It is important that sponsors discuss their approach with FDA at the trial planning stage and include the overall strategy for handling different intercurrent events and the associated analytical approach in the statistical analysis plan.

Missing data are data that would be meaningful for the analysis of a given estimand but were not collected.[31] The definition of missing data depends on how intercurrent events are handled. To impute missing data, statistical approaches should reflect the uncertainty about the nature of the missing data. Single imputation approaches are discouraged. Prespecified sensitivity analyses are recommended to assess the robustness of the primary analysis results.

G. Expedited Programs

FDA encourages the development of non-opioid analgesic products and novel study designs. Non-opioid analgesic development programs designed to avoid, eliminate, or reduce the use of opioid analgesics may be eligible for one or more of FDA's expedited programs, as applicable. FDA encourages early discussion of products that could avoid, eliminate, or reduce opioid use and may be suitable for participation in one of these expedited programs.

[30] See the ICH guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021).

[31] See ICH E9(R1).

The four broadly-applicable[32] expedited programs (fast track, breakthrough therapy, priority review, and accelerated approval) and their relevant criteria are described both in section 506 of the FD&C Act and in the guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014).[33] Although each program differs, they all offer some form of expedited review, either during the drug development stage or upon receipt of the marketing application.[34]

Although accelerated approval is one of the expedited programs discussed in the guidance, FDA has not had experience with an analgesic approval based on a surrogate endpoint that is reasonably likely to predict clinical benefit, as would be consistent with accelerated approval.[35] Given that pain intensity is a subjective experience that can be directly reported only by the patient, it would be difficult to envision how surrogate or intermediate endpoints could be used to predict analgesic effect. However, we encourage exploration of potential biomarkers, such as pharmacodynamic/response biomarkers, that may facilitate participation in an expedited program. In addition, consistent with applicable statutory criteria, FDA will consider a non-opioid analgesic's abuse or misuse potential and its risk profile relative to available opioid analgesics to determine whether the application qualifies for fast track or breakthrough designation during development or for priority review upon receipt of the marketing application.

[32] Two other expedited programs described in section 506 of the FD&C Act (21 U.S.C. 356), limited population pathway for antibacterial and antifungal drugs and regenerative medicine advanced therapies, apply to a narrower set of applications and are described in separate guidances.

[33] See also the draft guidances for industry *Expedited Program for Serious Conditions — Accelerated Approval of Drugs and Biologics* (December 2024) and *Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway* (January 2025). When final, these guidances will represent FDA's current thinking on these topics.

[34] In addition to the programs outlined above, the Breakthrough Devices Program may be available for certain nonaddictive medical products to treat pain (see section 515B of the FD&C Act (21 U.S.C. 360e-3)). The Breakthrough Devices Program is a voluntary program for certain medical devices and device-led combination products that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. The guidance for industry and Food and Drug Administration staff *Breakthrough Devices Program* (September 2023) outlines the criteria for designation as a breakthrough device as well as the policies FDA intends to use to implement the program.

[35] See section 506(c) of the FD&C Act and 21 CFR 314.500 et seq. For drugs granted accelerated approval, postmarketing trials have been required to verify and describe clinical benefit.