Development of Non-Opioid Analgesics for Acute 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DRAFT GUIDANCE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)

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TABLE OF CONTENTS

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I. INTRODUCTION

This guidance is written in response to the statutory requirements of section 3001(b) of the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act, which directs the Food and Drug Administration (FDA) to issue or update existing guidance to help address challenges to developing nonaddictive medical products to manage pain. In keeping with the mandate of section 3001(b), and considering the severity of the ongoing opioid crisis, this guidance is also intended to assist sponsors in the development of alternatives to opioids for the management of acute pain. Accordingly, this guidance addresses FDA's current thinking about three specific topics: development of non-opioid analgesic products for acute pain, labeling claims, and expedited programs as they pertain to this purpose.

This guidance does not address the management of chronic pain, which will be the focus of a future guidance. This guidance also does not address the development of opioid products.

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[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. You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2021-N-0556 (available at https://www.regulations.gov/docket?D=FDA-2021-N-0556). See the instructions in that docket for submitting comments on this and other Level 2 guidances.

II. BACKGROUND

FDA is committed to using its authorities to take measures targeted to combat the opioid crisis. In 2017, FDA announced its intention to focus on four priorities, two of which directly relate to this guidance: (1) fostering the development of novel analgesic drugs and (2) decreasing opioid analgesic exposure and preventing new addiction.[2] To address these two priorities, and consistent with our mandate under SUPPORT Act section 3001(b) to issue guidance in this area, FDA is publishing this guidance.

For context, it is important to set forth FDA's general understanding of pain and specific definition of acute pain. For the purposes of this guidance, *acute pain* is defined as pain, lasting up to 30 days, typically in response to some form of tissue injury, such as trauma or surgery.[3]

This understanding informs the development of this guidance, which describes FDA's current thinking about three aspects of non-opioid analgesic drug development:

- The drug development program appropriate for a non-opioid analgesic to support an indication for the management of acute pain ("acute pain indication")
- The availability of claims in labeling of non-opioid analgesic products for acute pain regarding elimination or reduction of opioid use and the data needed to support those claims
- The use of expedited programs to support the development program for non-opioid analgesics to manage acute pain

III. DEVELOPMENT OF NON-OPIOID ANALGESICS

A. Non-Opioid Analgesic Product Development for Acute Pain

1. General Considerations

Indications for analgesics intended to manage acute pain can be general or specific. A general acute pain indication would reflect the expectation that the product will be effective for most types of acute pain.[4] The number of adequate and well-controlled clinical trials needed to support a general acute pain indication depends on the mechanism of action of the drug, the

[2] 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] This definition of *acute pain* is consistent with the International Association for the Study of Pain's definition, which is as follows: "Acute Pain is generally accepted as being of recent onset and limited short duration. It usually has a temporal (follows immediately after surgery/trauma) and causal (has a known cause) relationship to injury or disease. The intensity of acute pain is greatest at the onset of injury, but with healing pain intensity reduces."

[4] Because of interindividual differences, a product indicated for general acute pain, and expected to be appropriate to manage many kinds of acute pain, does not mean the product is expected to be effective for every patient.

populations studied, and the degree to which the available information would support the efficacy across the acute pain settings in which the product would be used. Products with well-established analgesic mechanisms of action may be able to obtain a general acute pain indication when supported by at least two clinical trials, each in a different pain population. For example, a novel nonsteroidal anti-inflammatory drug with two successful clinical trials in postoperative pain, one following bunionectomy and one following herniorrhaphy, may be suitable for a general acute pain indication. In contrast, products with novel mechanisms of action are likely to require clinical trials in more than two different pain populations to support a general acute pain indication. As it is generally not feasible to study all possible populations that fall within a general acute pain indication, it may be necessary to include language in labeling describing the limitations of the indication.

A specific acute pain indication reflects results from studies in a specific pain population (e.g., postsurgical analgesia following hernia repair). Some products may be suitable only for specific populations (e.g., topical analgesic for underlying soft tissue injury). A specific pain-type indication generally requires evidence from at least two adequate and well-controlled clinical trials.

Some sponsors may initially choose to demonstrate effectiveness of a particular drug in a specific pain-type population and then subsequently pursue additional specific indications, or a general indication, with additional trials in other acute pain settings to support broader use. In both of these scenarios, additional patient populations and types of pain can be studied and study results submitted as efficacy supplements to broaden the indication. In many cases, for both additional specific indications or to expand the indication from a specific pain indication to a general indication, one additional adequate and well-controlled efficacy trial may be sufficient.

2. Trial Design

Clinical trials to support a finding of efficacy for a non-opioid analgesic should be randomized, double-blind, superiority trials. The trials should include repeat-dose design as appropriate. Treatment duration should be based on the pain model used to support the proposed indication sought but should be no fewer than 24 hours for products that are not limited to a single dose. The primary endpoint should be based on the change in pain intensity over a suitable time period based on the pain model used in the trial and the product's expected duration of pain relief; however, the time period assessed does not have to be for the full duration of the pain. After evaluation of the primary endpoint, we recommend continued evaluation of both safety and efficacy, for evidence of sustained effect, which may be relevant to acute pain lasting up to 30 days.

For acute pain, it is common to use an analysis such as the Sum of Pain Intensity Difference (SPID) over a prespecified time period that reflects the expected duration of treatment effect of the product. Demonstrating superiority to a comparator is important in non-opioid analgesic trials because the primary endpoint, pain intensity, can be influenced by study design factors such as the use of rescue medication and placebo effect. As a result, a noninferiority trial showing no difference between analgesic treatments could mean that neither product worked in

that study.[5] Suitable comparators for the superiority study could include placebo or another analgesic if the new product is expected to be more effective than the comparator analgesic. In some cases, the test treatment and control (placebo or a different analgesic drug) may also be added to background therapy (an "add-on study"). The background therapy could be specified or caregiver selected.

Protocols should prespecify allowed rescue medications. Depending on the pain condition being studied, rescue medications might include nonsteroidal anti-inflammatory drugs or, in clinical settings in which opioids are typically required for adequate pain relief, opioids may be considered. Protocols should also prespecify the frequency, amount, and threshold of pain at which allowable rescue medication(s) can be administered. This is particularly important in placebo-controlled trials where increased use of rescue medication in the control group may diminish the study drug's treatment effect, leading to a conclusion of ineffectiveness. The statistical analysis plan should describe how discontinuations caused by inadequate pain control will be handled. The concept of rescue use, including the prospective plan in the effectiveness analysis to assess its use, as well as how the data support the overall indication, is important and is discussed further in section III. A. 3. below, under Secondary Efficacy Endpoints.

3. Outcome Measures to Obtain an Acute Pain Analgesic Indication

Primary Efficacy Endpoint

In general, an assessment of pain intensity is the primary outcome measure to establish the efficacy of an analgesic intended to manage acute pain. Efficacy endpoints (e.g., change in pain intensity) in a non-opioid analgesic trial should reflect a direct rating of pain intensity by the subject for all settings in which the subject can communicate in a reliable manner. We recommend using a well-defined and reliable patient-reported outcome measure of the subject's pain intensity.[6] The selected instrument should have the subject assess their pain at the time of the assessment (i.e., without using a recall period). Generally, a numerical rating scale is the appropriate measure.

We recommend that sponsors take frequent pain intensity measurements at preselected time points during the trial to accurately measure the effect of a non-opioid analgesic and that effect over time (e.g., every hour for X number of hours, then every 4 hours for X number of hours). All pain intensity measurements, including at baseline, should be obtained before rescue drug administration. In general, the frequency of pain intensity assessment is greater with initial drug administration, early post-event (e.g., post-injury or surgery), when pain may be more intense. The primary efficacy analysis should compare the SPID between treatments at a prespecified time point that, at a minimum, includes the duration of drug effect, and may extend beyond this

[5] *See* 21 CFR 314.126(b)(2)(iv) (providing "Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective.") For more information about noninferiority trials, 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.

[6] For a thorough discussion of patient-reported outcome measures, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009).

duration. For example, a non-opioid analgesic with an expected 4- to 6-hour duration of action might have the primary efficacy analysis performed at 24 hours post-dose ($SPID_{24}$), but secondary efficacy analyses may also be performed at 6 and 12 hours post dose ($SPID_6$ and $SPID_{12}$, respectively) to evaluate pain control during the recommended dosing interval.

We discourage using a primary endpoint that is based on pain relief (i.e., decrease in pain) rather than pain intensity (i.e., how bad the pain is), as pain relief scales require subjects to report current pain relative to their prior pain experience and may be influenced by other factors such as concurrent adverse reactions, and may be limited by patients' ability to recall their prior experience of pain. Additionally, sponsors should generally avoid using composite scales that are composed of multiple domains (e.g., pain, function, sleep) as the primary outcome measure in a non-opioid analgesic trial. Such multiple domain scales may be difficult to interpret across a population, as the same change in overall score can be based on differing patterns of response to the individual domain scores. For example, an overall score may be higher at baseline, reflecting poor sleep (with functional consequences), with improvement in the score reflecting improvement in sleep, such as might be seen with a sedating drug that does not provide substantive pain control. Multi-item scales, where the items all relate to pain (e.g., pain at rest or with movement), may be useful depending on the type of pain being studied.

Secondary Efficacy Endpoints

Secondary outcome measures are important to fully characterize the efficacy of a non-opioid analgesic and should support the primary efficacy endpoint. These secondary outcome measures include measurement of time to onset of pain relief and time to rescue or request for next dose of the study drug. Other informative secondary outcome measures include assessment of use of rescue medications, physical function, and patient global impression of change of pain.

To measure time to onset of pain relief, FDA has accepted the "two stopwatch method." In this method, patients are instructed to stop the first stopwatch when they first perceive any analgesic effect and instructed to stop the second stopwatch when they perceive a meaningful amount of analgesia, which may be translated into a description in labeling of median time to meaningful pain relief. FDA remains open to discussion and consideration of approaches beyond the "two stopwatch method" to assess the time to onset of pain relief, which is particularly important to establish if there is an expectation of rapid onset of action (e.g., intravenous formulation).

For all acute pain non-opioid analgesic studies, it is particularly important that sponsors record the following information:

- The type and amount of rescue medication used, including dose, frequency, and duration
- The time that the study drug or rescue medication was administered
- The pain intensity measurements before the rescue medication was used and throughout the dosing interval (e.g., evaluating SPID over the course of expected duration of action)

Use of rescue medication can inform important properties of the drug and should be carefully considered in the design of the study so as not to jeopardize the validity of the study. A sooner-than-expected first use of rescue medication may suggest that the investigational drug has a delayed onset of pain relief. Time to second use of rescue medication may be informative when considering dosing interval for the investigational drug and supplement knowledge of the drug's pharmacokinetic properties. If the time to second use of rescue medication is earlier than expected based upon drug exposure, waning efficacy can be considered a potential issue.

Endpoints Associated with Reducing or Eliminating Opioid Use

As discussed further below, total elimination of opioid or a numerical reduction in the number of doses, dose per day, or duration of opioid use may support the efficacy of the investigational drug in alleviating pain. In order to support a clinical benefit of a reduction in opioid use that would be described in labeling, sponsors should demonstrate a direct patient benefit, such as clinically meaningful reduction in the incidence and/or severity of opioid-induced adverse reactions. See section III. B. below.

Biomarkers

FDA is not aware of any biomarkers that are useful in developing pain management products, but we welcome feedback on this issue. If sponsors identify a way to use biomarkers in any aspect of a clinical trial associated with non-opioid analgesics for acute pain, we are interested in engaging on this topic.

4. Safety Considerations–Clinical Trial Elements

When monitoring safety during clinical trials, sponsors should consider the nature of the drug and the trial population. Sponsors may also need to include subject discontinuation and/or study stopping criteria in protocols, depending on the expected safety profile of a non-opioid analgesic.

Appropriate assessment of both effectiveness and safety relies on accurate and complete capture of the reason for subject discontinuation. Sponsors should assure that when a subject discontinues study drug or withdraws from the trial that the specific reason is obtained. Investigators should be prompted to provide detailed information, with specific causes rather than report terms such as "other," "subject request," "investigator decision," or other such nonspecific categories. Sponsors also should ensure that case report forms are designed to accurately capture the reason for patient discontinuation.

The size of the safety database needed to support approval for an acute pain indication depends on a number of factors, including whether the drug is a new molecular entity or a reformulation of an approved drug substance. In addition, a nonclinical safety finding or safety data from early clinical studies suggesting a potential serious adverse reaction may necessitate enlargement of the safety database to better define the safety profile of the proposed product. Safety assessments should continue as appropriate after dosing is completed, with consideration of patient population and setting (i.e., inpatient versus outpatient).

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

B. Potential Claims in Labeling for Non-Opioid Analgesic Products for Acute Pain That Eliminate or Reduce Opioid Use and Data Needed to Support Those Claims

1. FDA Thinking Regarding Concept of "Opioid-Sparing"

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 eliminating or reducing the need for opioid analgesics as discussed in section III. B. 2. below.[7] For drugs that are already approved and for those that are seeking initial approval, considerations in describing elimination or reduction in the need for opioid analgesics are similar.

2. Reductions in the Use of Opioid Analgesics That May Merit Description in Labeling

There are several ways in which a non-opioid analgesic may show benefit in reducing opioid use that would merit description in labeling:

- Eliminating patient use of opioid analgesics in some or all patients in a pain setting in which use of opioids would typically be required to alleviate pain

- Providing adequate analgesia such that the patient can be discharged from the health care facility without opioid analgesics when patients would be expected to be discharged with opioid analgesics

- Showing a direct patient benefit related to reduced opioid analgesic use, such as a clinically meaningful reduction in opioid-associated adverse reactions or earlier functional recovery (e.g., earlier ability to participate in physical therapy with earlier regain of ambulation)

In each of these scenarios, data should support a finding that the non-opioid and opioid have comparable effects on pain.

a. Product eliminates patient use of opioid analgesics

Exposure to an opioid analgesic presents a risk of addiction, misuse, or abuse. In addition to the risk of addiction, opioid use also may cause serious adverse reactions, including overdose, and death. Therefore, a non-opioid analgesic for acute pain that completely eliminates the need for

[7] This view is consistent with feedback provided at the November 15, 2018, Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee. See https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-15-2018-meeting-anesthetic-and-analgesic-drug-products-advisory-committee-meeting.

an opioid in a setting in which opioid-level analgesic would be otherwise necessary would have the greatest impact on reducing the risk of opioid addiction. In addition to reducing the risk for the patient, the absence of opioid analgesics in the home lessens access to others in the same residence who may seek opioid analgesics for misuse or abuse.

If a sponsor can show that a product eliminates the need for an opioid analgesic in a statistically significant number of patients in a setting in which opioids are routinely required for adequate acute pain control, this finding could be sufficient to support description in labeling. In such circumstances, labeling that describes analgesia comparable to or better than the comparator opioid may be appropriate.

b. Product enables patient discharge without opioid analgesics

As with products that eliminate opioid use, if a sponsor demonstrates that a non-opioid analgesic product eliminates the need for an opioid to manage acute pain at discharge from a health care facility or other outpatient settings, when opioid use post-discharge is routinely needed, this also could be considered adequate to support description in labeling. Additional assessments after discharge would be required to confirm patients' pain can be managed without opioids. Reducing the supply of prescription opioid analgesics in the home reduces the risks of misuse and abuse by both the patient and others within the home. Labeling that describes these findings may be appropriate.

c. Product reduces patient exposure to opioid analgesics with direct clinical benefit to the patient

Apart from discharge by a health care facility without opioids, reduction in dosage and/or duration of opioid use alone is not likely to be adequate to support description in labeling. To include a reduction in opioid use in labeling, the reduction claim should be associated with a direct patient benefit such as (1) reduced time to recovery of function, such as more rapid mobility and/or earlier ability to participate in rehabilitation or other clinically meaningful functional outcomes, or (2) a relevant decrease in opioid-related adverse reactions such as less sedation, fewer gastrointestinal side effects (such as constipation), or other adverse reactions. If these types of clinical benefits are adequately demonstrated in clinical trials, language in the labeling delineating these benefits could be included.

3. Data to Support Language in Labeling Describing Clinically Meaningful Reductions in Opioid Analgesic Use

To support language describing clinically meaningful reductions in opioid analgesic use in product labeling for any of the categories described above, sponsors should provide data from at least two adequate and well-controlled trials. As described in section III. B. 2. above, examples of clinically meaningful outcomes include not requiring opioids for a pain model where opioid use is usually required, or, where use of opioids is still needed, showing reduced opioid dose requirements in concert with either a shortening of time to mobility (e.g., following orthopedic surgery) or a reduction in the frequency of major complications of opioid treatment, such as delirium in an elderly population or a reduction in opioid-related adverse reactions.

FDA also encourages sponsors to include open-label extensions with follow-up assessment of opioid analgesic utilization (e.g., 30 days after discharge following a surgical procedure) to assess whether patients have been taking opioid analgesics during the period of extension.

FDA does not recommend observational study designs or exclusive use of electronic health care data (e.g., electronic health record or administrative claims data) to support labeling language describing clinically meaningful reductions in opioid analgesic use. Electronic health care data are not sufficiently able to measure factors that may drive selection of patients for the investigational versus the control treatment. Likewise, routinely collected health care data (e.g., administrative claims data) are insufficient to ascertain primary endpoints, such as pain control, level of function, actual opioid use, and adverse effects.

However, incorporating electronic health care data may be useful in other respects. For instance, such data may be valuable (1) in assessing opioid analgesics dispensed at discharge and persistent prescribed opioid analgesic dispensing, (2) in understanding current practices and standards of pain management in specific clinical settings, and (3) in identifying patients who may be eligible for study participation. We remain interested in feedback on ways in which these data could be useful to support the development of non-opioid analgesic products.

We recognize that we are not addressing all aspects of clinical trial design for products that may reduce the use of opioid analgesics in a way that may merit description in product labeling, and we invite comment on this area of clinical trial design in response to this guidance. We also encourage sponsors of any non-opioid analgesic for acute pain seeking a claim of opioid replacement or reduction in labeling to have early and regular discussions with FDA to help ensure the use of adequate and interpretable assessments of treatment benefits that are consistent with a drug's mechanism of action.

C. Expedited Programs

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

These expedited programs and their relevant criteria are described in the guidance for industry *Expedited Programs for Serious Conditions–Drugs and Biologic*s (May 2014). The applicable expedited programs include fast track, breakthrough therapy, priority review, and accelerated approval. Although each program differs, they all offer some form of expedited review and guidance for sponsors for drug development programs.[8]

[8] In addition to the programs outlined above, the Breakthrough Devices Program may be available for certain nonaddictive medical products to manage pain. (Federal Food, Drug, and Cosmetic Act § 515B (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*

382 FDA has not had experience with an analgesic approval based on a surrogate or intermediate
383 endpoint that is reasonably likely to predict clinical benefit, as would be consistent with
384 accelerated approval.[9] Given that pain intensity is a subjective experience that can only be
385 directly reported by the patient, it is difficult to envision how surrogate or intermediate endpoints
386 could be used to predict analgesic effect. However, consistent with applicable statutory criteria,
387 FDA will consider a non-opioid analgesic's abuse or misuse potential and its risk profile relative
388 to available opioid analgesics to determine if the application qualifies for fast track or
389 breakthrough designation during development, or for priority review upon receipt of the
390 marketing application.

Program (December 2018) outlines the criteria for designation as a breakthrough device as well as the policies FDA intends to use to implement the program. The considerations set forth in that guidance document apply to FDA's review of devices as nonaddictive methods to manage pain.

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