Guidance for Industry
Analgesic Indications:
Developing Drug and Biological Products

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Guidance for Industry¹
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This draft guidance, when finalized, will represent the Food and Drug Administration’s (FDA’s) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides recommendations to sponsors on the development of prescription drugs² that are the subject of new drug applications (NDAs) for the management of acute and chronic pain as well as the management of breakthrough pain (hereafter analgesic development).³ Specifically, this guidance focuses on clinical drug development and trial design issues and chemistry, manufacturing, and controls (CMC) concerns that are unique to the study of acute, chronic, and breakthrough pain and the labeling considerations for analgesic drugs. This draft guidance is intended to serve as a focus for continued discussions on relevant issues among the Division of Anesthesia, Analgesia, and Addiction Products, pharmaceutical sponsors, the academic community, and the public.⁴

This guidance does not discuss nonclinical drug development, because we have not identified nonclinical concerns unique to analgesic development.

This guidance does not specifically address all syndromes in which pain is a component such as dysmenorrhea, migraines, or irritable bowel syndrome. Sponsors seeking to develop drugs for these syndromes should consult with the appropriate review division. This guidance also does

¹ This guidance has been prepared by the Division of Anesthesia, Analgesia, and Addiction Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

² For the purposes of this guidance, all references to drugs include both human drugs and therapeutic biological products regulated within CDER unless otherwise specified.

³ For the purposes of this guidance, analgesics are defined as drugs that treat the symptom of pain, but not necessarily the underlying etiology of the pain.

⁴ In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during analgesic development.
not discuss general issues related to statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.\(^5\)

FDA’s guidance documents, including this guidance, 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 guidances means that something is suggested or recommended, but not required.

**II. BACKGROUND**

Pain can be categorized according to its duration, acute or chronic, as well as based on other characteristics, such as breakthrough pain, acute episodes of pain that occur on a background of well-controlled, chronic pain. Pain is subjective in nature and is measured by patient self-reporting of its intensity, and other subjective qualities.

For the purpose of this guidance, *acute pain* is defined as pain that is self-limited and generally requires treatment for no more than up to a few weeks (e.g., postoperative or acute musculoskeletal pain). Even in the setting of acute pain, analgesics generally are used repeatedly over some period of time and not as single-dose treatments. Therefore, although it is important to understand the single-dose analgesic effects of a drug, unless a drug is intended solely for single-dose use, single-dose studies are not considered sufficient to establish the efficacy and safety for drugs indicated for treating acute pain.

*Chronic pain* is defined as either pain persisting for longer than 1 month beyond resolution of the underlying insult, or pain persisting beyond 3 months. In the context of this guidance, chronic pain refers not only to chronic pain in the terminally ill, but also to chronic pain of various etiologies in persons who are otherwise healthy (e.g., post-traumatic pain, osteoarthritis) or in persons with underlying diseases or conditions that have pain as a prominent manifestation (e.g., chronic low back pain, spinal cord injury, or diabetic peripheral neuropathy), which is anticipated to persist for 3 months or longer.

Pain can be further subdivided into whether the origin of the pain is *nociceptive*, *neuropathic*, or of mixed nociceptive/neuropathic origin. *Nociceptive pain* is defined as pain arising from stimulation of somatic or visceral nociceptors and is subdivided into visceral and nonvisceral pain. Visceral pain includes such conditions as pancreatitis, renal colic, and postoperative visceral surgery, whereas nonvisceral pain encompasses conditions such as postoperative orthopedic surgery, fractures, and other musculoskeletal pain. *Neuropathic pain* is defined as

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\(^5\) We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm).
pain initiated or caused by a primary lesion or dysfunction in the nervous system. There are a number of neuropathic pain syndromes, based on pathogenesis, affected pathways, and physiological course. In general, neuropathic pain syndromes can be classified as either peripheral (when the lesion or dysfunction affects the peripheral nervous system) or central (when the lesion or dysfunction affects the central nervous system). Peripheral neuropathic pain syndromes include but are not limited to painful diabetic peripheral neuropathy, postherpetic neuralgia, complex regional pain syndrome, and HIV-associated neuropathy. Central neuropathic pain conditions include but are not limited to postspinal injury pain and poststroke pain.

*Breakthrough pain* is defined as a transient flare of pain occurring in opioid-tolerant patients experiencing persistent pain otherwise controlled with around-the-clock maintenance opioid therapy consisting of an equivalent of at least 60 milligrams (mg) of morphine per day or an equianalgesic dose of another opioid for 1 week or longer.

The terms *mild, moderate,* or *severe* are often used in a clinical setting to describe pain severity. Although subjective, these terms are commonly used and understood both by health care providers and patients. The terms generally correlate with pain scores on average within the clinical context under evaluation. However, it is understood that when patients report severe pain following a dental extraction, this measurement may not be qualitatively the same as when patients report severe pain following abdominal surgery.

### III. ESTABLISHING INDICATIONS AND CLAIMS FOR ANALGESICS

We encourage sponsors to state the indications being sought for their analgesics before phase 3 studies are initiated, and to discuss these indications with the FDA as early as feasible. Suggested approaches for establishing analgesic indications are provided in the following text, which is divided into sections that discuss procedures for: (1) new molecular entities (NMEs); (2) reformulations of approved drugs; (3) add-on or adjunctive indications; and (4) additional claims.

For the purposes of establishing an analgesic indication, the severity of the expected pain intensity based upon the underlying cause should be taken into consideration and weighed against the risks of the drug. Therefore, drugs associated with greater risks may be indicated for pain of great enough severity to warrant those risks and that may not be expected to be adequately treated by drugs or drug dosages used for pain of lesser severity (e.g., cancer pain or postoperative pain following major abdominal surgery).

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7. See the draft guidance for industry and review staff *Target Product Profile — A Strategic Development Process Tool.* When final, this guidance will represent the FDA’s current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
A. NMEs

1. Introduction

NMEs should have development programs that explore the analgesic drug’s safety and
effectiveness in a variety of clinical situations. We encourage sponsors to explore the efficacy of
these drugs to best assess in which settings the drug may be useful. Resulting information may
inform the indication and ensure that safety information is gathered in studies of patient
populations likely to be exposed to the drug after approval. The final proposed indication should
reflect the safety and efficacy of the drug based on appropriately designed clinical studies. The
INDICATIONS AND USAGE section of labeling should be supported by language describing
the specific conditions studied in the CLINICAL STUDIES section. In general, as described
below, a finding of efficacy for an NME analgesic that is to be used to treat a specific pain
condition should be supported by at least two adequate and well-controlled studies, depending on
the condition.8

2. Specific/Narrow Pain Indications

a. Condition- or population-specific

For specific/narrow indications that are determined to be appropriate based on the safety and
efficacy of the new drug product, such as the pain of osteoarthritis, chronic low back pain, or
pain of fibromyalgia, two clinical trials in the specific condition typically will be adequate to
support a finding of efficacy for that indication. Relatively narrow indications may be
appropriate for drugs that have shown clinical efficacy in only limited therapeutic settings, or
when substantial safety concerns result in an acceptable risk-benefit analysis only in limited,
defined situations of use.

New routes of administration and new patient populations with different risk-benefit
considerations or a population that might be expected to have increased risk from the drug also
can form the basis for narrow indications. An example is a drug intended only for intrathecal
therapy for chronic pain. Given the risks associated with chronic intrathecal therapy, a possible
indication might be: For the management of chronic pain in patients for whom intrathecal
analgesic therapy is warranted. An example of a new patient population is a drug intended only
for use in patients who have developed opioid tolerance as a result of prior exposure to opioids
as this may be the only population that can tolerate a new formulation with doses larger than
would be safe in an opioid-nontolerant population.

Some drugs, whether an NME or well characterized, can pose special concerns based on
formulation or toxicity profile. One example is the use of modified-release opioids for chronic
cancer pain. These drugs can contain large amounts of opioid in each dose resulting in serious
safety concerns including those associated with accidental overdose or misuse. We recommend
that the indications for drugs that pose special concerns specifically reflect the narrow patient
population that would most appropriately be treated with the drug (see section IV.C.5.b., Class
labeling).

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8 See section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); see, for example, 21 CFR 314.126.
b. Breakthrough pain

For an NME whose sponsor is seeking an indication for the treatment of breakthrough pain, generally two clinical trials that demonstrate efficacy in opioid-tolerant subjects experiencing persistent pain otherwise controlled with maintenance doses of around-the-clock opioid therapy, including at least 60 mg morphine equivalents per day, should be adequate to support a finding of efficacy.

3. General Pain Indications

a. General acute pain

For an indication of the treatment of general acute pain, two successful trials in nociceptive pain, one in visceral pain and one in nonvisceral pain, generally will be considered to be adequate. In this setting, visceral pain includes such conditions as acute pancreatitis, renal colic, and postoperative visceral surgery, whereas nonvisceral pain encompasses conditions such as postoperative orthopedic surgery, fractures, and other acute musculoskeletal pain. Although the study of both visceral and nonvisceral pain likely will capture the majority of acute pain situations, factors such as the type of tissue affected and pain intensity should be taken into consideration when deciding if the population is appropriate to support a general pain indication or whether additional or alternate trials may be necessary. Overall, for a drug intended for outpatient use, at least one trial should be in outpatients, and for a drug intended for inpatient use, at least one trial should be in an inpatient setting.

b. General chronic pain indications

Chronic pain may result from a number of different conditions with different underlying pathophysiologic etiologies, and efficacy in reducing pain in one condition may not predict efficacy in others. The following represent options for chronic pain indications.

- Neuropathic Pain
  
  - Peripheral Neuropathic Pain. Typical peripheral neuropathic conditions include diabetic peripheral neuropathy; post-herpetic neuralgia; HIV-associated neuropathic pain; post-traumatic/postoperative peripheral neuropathy; and chemotherapy-associated peripheral neuropathy. Two successful trials in any one condition typically will be appropriate for approval of an indication for that particular condition. One additional successful trial in a second condition also may be appropriate for approval of an indication for this second condition. However, for the indication of the treatment of peripheral neuropathic pain, sponsors should conduct one trial in each of at least three separate peripheral neuropathic conditions (for a total of at least three trials) to ensure a reasonable likelihood that efficacy will be generalizable across peripheral neuropathic pain conditions.
- Central Neuropathic Pain. For a stand-alone indication of the treatment of central neuropathic pain, generally sponsors should conduct at least two trials, each trial in a different central neuropathic condition such as the pain of spinal cord injury, poststroke neuropathic pain, or the pain of multiple sclerosis.

- General Neuropathic Pain. For an overall indication of the treatment of neuropathic pain (both central and peripheral), the recommendations for peripheral neuropathic pain should be fulfilled (i.e., successful trials in each of at least three separate peripheral neuropathic conditions), as well as one successful trial in one central neuropathic condition for a total of at least four trials in four distinct conditions.

- Chronic Musculoskeletal Pain. If seeking an indication for the treatment of osteoarthritis, chronic low back pain, or other specific musculoskeletal conditions, sponsors should conduct two successful trials in any one condition for an indication for that condition. However, for the more general indication of the treatment of chronic musculoskeletal pain, sponsors should conduct two successful trials in one condition plus a successful trial in another musculoskeletal condition (for a total of at least three trials in at least two conditions).

- Chronic Pain. To obtain approval for the broad indication of the treatment of chronic pain, sponsors should meet the recommendations for general neuropathic pain (i.e., at least four trials per four conditions including one in central neuropathic pain) as outlined above. In addition, sponsors should conduct two successful trials in one non-neuropathic pain condition plus one successful trial in each of two additional non-neuropathic pain conditions (at least four trials per three non-neuropathic conditions). Non-neuropathic pain conditions that are suitable for this purpose include osteoarthritis, chronic low back pain, chronic visceral pain, cancer pain, and fibromyalgia. Thus for an overall indication of the treatment of chronic pain, sponsors should conduct at least eight trials in seven conditions. However, we encourage sponsors to study as many conditions as possible to more fully characterize the properties and potential populations likely to benefit from treatment.

We encourage sponsors with analgesic drugs for which they are seeking general pain indications (e.g., treatment of the pain of peripheral neuropathy, treatment of the pain of neuropathy, or treatment of musculoskeletal pain) to discuss those development programs with the review division early in development. This is particularly important for sponsors whose drugs fall within well-recognized analgesic drug classes such as opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), or local anesthetics, because additional flexibility and individualization of the development programs may be possible.

B. Reformulations of Approved Drugs

For reformulations of approved analgesics, if an NDA is intended to be submitted as a 505(b)(2) application that references an analgesic listed drug, reliance on the FDA’s previous finding of safety and effectiveness for the listed drug and one adequate and well-controlled trial (in addition to comparative bioavailability studies against the listed drug) may be sufficient to support the
change from the listed drug. This includes modified-release reformulations of a drug previously
approved as an immediate-release product. For proposed products that include a new route of
administration, a new indication, or a new population, sponsors should conduct two adequate and
well-controlled trials to support a finding of efficacy, but consideration may be given to alternate
proposals with adequate justification. In general, whether the finding of analgesia should be
replicated in specific patient populations (i.e., subjects with particular types of pain) versus
across patient populations depends on how much is known about the pharmacology of the drug
under development.\(^9\)

C. Add-On or Adjunctive Indications

There may be situations in which drugs are studied as add-ons or adjunctive therapy in subjects
receiving concomitant treatment with an existing standard of care. This situation may be
appropriate for drugs expected to have an effect only in conjunction with concomitant treatment
or in patient populations that cannot be studied without the underlying therapy. In cases where
the efficacy data come from such adjunctive use, the drug would likely receive an indication as
an adjunctive therapy in the setting under which it was studied).

D. Additional Claims

Additional claims of treatment benefit based on clinical domains relevant to analgesia may be
appropriate for some clinical populations that are defined by those domains. Claims of treatment
benefit should represent findings that are not directly a result of a change in pain, but if subjects
sleep better merely because they have less pain, the improved sleep is not a direct positive effect
of the drug. For example, fibromyalgia is a syndrome that includes pain as well as fatigue and
trouble sleeping. A properly designed evaluation of sleep during a clinical trial in subjects with
fibromyalgia may demonstrate positive effects for pain as well as sleep. In contrast, subjects
treated with a sedating analgesic may sleep more, but this may not represent improved sleep, and
these subjects may experience the sedating effects during the day as well. Replicated findings
from adequately designed studies incorporating instruments demonstrating substantial, clinically
meaningful improvement can support such claims.

Early in drug development, sponsors seeking treatment benefit claims in addition to analgesia
(e.g., improved physical or emotional functioning) should determine whether a well-defined and
reliable patient-reported outcome (PRO) measure exists to assess and measure the concept of
interest and context of use or whether a new measure should be developed. The guidance for
industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support
Labeling Claims delineates the evidentiary standards by which the FDA reviews a measure for
its adequacy to support labeling claims. If additional treatment benefit claims are sought, it is
important to also assess the drug’s effect on pain (i.e., its analgesic effect) in the same studies,
because it is not possible to interpret the effect of treatment on distal concepts (e.g., less
constipation) without also evaluating the core symptom under investigation (i.e., pain). We

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\(^9\) To the extent that an applicant seeks to rely for approval on the FDA’s previous finding of safety or effectiveness
for a listed drug and/or published literature, the application must be submitted under section 505(b)(2) of the FD&C
Act.
recommend that sponsors prespecify the analysis of endpoints to support additional claims, including methods to address multiplicity.

IV. DEVELOPMENT PROGRAM

Analgesic development involves important concepts that sponsors should consider during drug development, such as the duration of drug exposure for the treatment of acute and chronic pain and the subjective nature of pain intensity measurement. It is important that the spectrum of clinical studies planned during analgesic development provide an adequate characterization of the clinical, pharmacological, and, when feasible, pharmacodynamic behavior of the drug.

When developing drugs to treat acute and/or chronic pain, the anticipated duration of exposure to the drug, not other accepted definitions of acute and chronic pain that may appear in medical literature, should define the duration and extent of safety and efficacy data needed to support the marketing application. For the purpose of determining whether nonclinical and clinical safety data support only acute use or support chronic use, we consider drugs intended for chronic use as those that may be used for a total duration of 6 months or longer, continuously or collectively, over the course of an individual’s lifetime. We consider drugs intended to treat acute pain as drugs that do not meet the duration of exposure criterion for chronic pain.

The anticipated context of use should be used to determine how much data would be considered necessary to support the application. Applications for drugs intended for repeated intermittent use in patients with recurring conditions, such as chronic low back pain, should be supported by a larger, long-term safety database. Applications for drugs that could be used more than once in an individual for multiple, independent episodes of pain, where the total lifetime duration of treatment is less than 6 months, would not need as extensive a safety database. As the number of anticipated intervals of short-term use increases, the distinction between acute and chronic use becomes less clear. In such cases, the sponsor should discuss the size of the safety database with the FDA early in development.

A. General Considerations

1. Early Phase Clinical Development

Generally, early analgesic development should be consistent with the standard phase 1 and phase 2 development objectives. Pharmacokinetic characteristics and tolerability should be explored in appropriate volunteers or stable, relatively healthy patient populations. One special consideration to keep in mind when planning early trials of analgesics when dosing is less certain is that pain is a highly activating stimulus. Doses of central nervous system (CNS) active drugs that are tolerated in subjects with pain may be overly sedating or may depress respiratory drive in healthy volunteers. Although subjects in some early studies of opioids can be protected from oversedation and respiratory depression with the use of opioid antagonists, there are no reversal or blocking agents currently available for other existing analgesic drugs or NMEs under development. Sponsors should monitor subjects for early signs of CNS or respiratory depression.
and appropriate interventions should be planned and specified in advance of initiating clinical trials.

We strongly recommend that sponsors include in the protocol detailed information for managing adverse events along with documentation of the immediate availability of staff capable of managing emergencies (e.g., trained in airway management). In general, reliance on transport to an emergency room as the primary support for emergency events may not be appropriate. Stopping criteria for ending further dosing of a dose level, or for discontinuing an individual from the study, should be included in all study protocols. Criteria should be based on the toxicity findings from nonclinical studies, as well as basic vital signs, physical exam, or laboratory parameters as appropriate to the situation. As always, but especially in the absence of any potential benefit for healthy volunteers, risks should be clearly and carefully delineated in the informed consent document. See 21 CFR parts 50 and 56.

For the earliest clinical studies during first-in-human exposure for any NME or reformulations of existing drugs that offer substantially greater risk than the original formulation, careful consideration should be given to dosing subjects within any dose cohort one at a time rather than simultaneously. The time between subjects should be based on the anticipated half-life of the drug. This is important for two reasons. For unexpected adverse events, initially dosing one subject at a time permits an opportunity to reevaluate the appropriateness of further testing of that dose and of the drug. For adverse events that require intervention, dosing subjects one at a time permits the staff to more closely monitor each individual subject.

Although there is no particular minimum number of studies to be conducted during phase 1 and phase 2, we strongly encourage sponsors to explore a broad range of doses to begin the evaluation for a dose response as well as to provide early information about the safety profile of the drug. Dropouts caused by adverse events can have a substantial negative effect on data collection and consequently on interpretation and adequacy of phase 3 efficacy results. During phase 2, it is important to explore ways to minimize adverse event occurrence, particularly adverse events that may occur during dose titration. Any information that leads to study designs that can minimize dropouts during the observation period (e.g., lengthening the titration period to minimize adverse event occurrence) may greatly improve the likelihood of success of phase 3 studies.

If possible, identification of a ceiling effect for efficacy during phase 2 can be informative for future study design considerations and for drug labeling. We encourage sponsors to explore exposure-response relationships for efficacy over a range of doses to help select the dose or doses for use in phase 3 trials.

Single-dose studies may provide useful information about several characteristics of the drug during phase 1 and phase 2, but are not considered adequate to support a finding of efficacy for a drug intended for multiple-dose use.
2. Drug Development Population

The intended target population for an analgesic indication depends on whether the drug is intended for use in acute or chronic pain, the severity of pain suitable for management with the drug, and the overall risk-benefit balance of the drug. For example, a drug intended for intrathecal use may be indicated for a patient population with pain that is severe and intractable and suitable for the inherent risks of an implantable pump. In contrast, a topical analgesic associated with minimal risk and indicated for the management of local pain may be indicated for a broader population.

3. Efficacy Endpoint Considerations

Because pain is a subjective experience, the choice of an adequate instrument to measure the primary endpoint is critical to demonstrating the efficacy of an analgesic. Therefore, it is important to consider whether a well-defined and reliable instrument exists or can be developed. It is also important that measures be based on scales or instruments that have been adequately developed for use in the population to be studied, and that the instruments be appropriate for use in the setting of a clinical trial to measure change over time. Novel instruments should have documented development and assessment of measurement properties available before use in phase 3 efficacy trials.10 The development of novel instruments should be discussed with the FDA early in drug development.11

Efficacy endpoints in an analgesic trial should reflect a direct rating of pain intensity by the subject for all settings in which subjects can communicate in a reliable manner. We recommend the use of a well-defined and reliable PRO measure of the subject’s pain intensity. We discourage an assessment that requires the subject to report on the concept of pain relief because the subject must compare their current state to a previous state, requiring additional mental processing of the overall experience. Additionally, pain relief scales can take into account not just a difference in pain intensity, but also consideration of how efficacy may be affected by adverse effects; therefore, the scales may represent a rating of a different concept for different subjects.

In case of young children or subjects who cannot provide self-report, observers (e.g., parents, caregivers) can report on observable indicators of disease or health condition through measurement of an observer-reported outcome (ObsRO). ObsRO concepts include only those events, behaviors, or signs that can be detected by an observer’s senses (i.e., wincing, crying, or squirming). An observer cannot validly rate a subject’s pain intensity and the FDA does not consider an instrument that requires an observer to do so to be well-defined or reliable. Similarly, a clinician-reported outcome instrument to be completed by the study investigator should be limited to those concepts that are observable.

10 See note 6, supra.

11 See the guidance for industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims for more detailed information.
Composite scales that are composed of multiple domains generally should be avoided as the primary outcome in an analgesic trial. Multidomain 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. Multi-item scales within a given domain may be useful. In contrast, the definition of a responder can include multiple components such as pain intensity, use of rescue, and ability to complete the study period and may be an acceptable primary outcome metric.

Pain intensity should be evaluated over an appropriate multiple-dose period suitable to support the indication sought. The endpoint instrument’s recall period for assessing pain should be appropriate for the type of pain studied and the planned study design. Generally, we recommend use of an instrument that asks the subject to assess his or her worst pain over a relatively short time period, and no longer than the past 24 hours, with the assessment occurring at the same time each day.

When pain intensity is the primary efficacy endpoint, it is important to take into consideration the use of rescue medication as a secondary outcome measure. (See additional discussion on this topic below.)

4. Safety Considerations

a. Clinical trial elements

The safety evaluation should reflect the fact that analgesics treat the symptom of pain, rather than cure or significantly modify an underlying disease or have a direct effect on survival.

- Monitoring safety during clinical trials. Safety monitoring during clinical trials should take into consideration the nature of the drug and the trial population. Care should be taken to adequately monitor for respiratory depression with opioids and other CNS depressants, particularly in early trials. For example, naltrexone blockade should be considered in phase 1 trials with healthy volunteers when higher doses of opioids are under evaluation. Monitoring oxygen saturation overnight can help ensure subject safety in early trials of non-opioid-tolerant subjects. Additional drug-specific monitoring plans can be determined based on nonclinical data and what is known about related compounds.

- Stopping criteria. The grading of toxicity in a clinical trial for the purposes of stopping criteria or creating the final report should be appropriate to the situation. For instance, the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE)\textsuperscript{12} were created for use in oncology clinical trials and generally are not appropriate criteria for grading toxicity in an analgesic trial, particularly early trials in healthy volunteers. The categories are broad and toxicities found to be higher than Grade 1, for most body systems, would be unacceptable during clinical trials for analgesics.

\textsuperscript{12} The CTCAE v4.0 includes adverse events applicable to all oncology clinical trials regardless of chronicity or modality (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).
Therefore, the sponsor should incorporate stopping criteria that are suitable for the circumstances of the clinical trial.

- **Reason for study discontinuation.** It is important that the reason for subject discontinuations in analgesic trials be captured accurately to provide the data for a risk-benefit assessment. In particular, all subjects with a designated reason for discontinuation of other, subject request, investigator request, or other nonspecific designations should have the actual reason for their discontinuation further explored and detailed. Many of these subjects may have discontinued because of lack of efficacy or adverse events. (See section IV.B.11., Statistical Considerations.)

  b. Safety database

The size of the safety database needed to support approval for an acute or chronic pain indication depends on a number of factors, including whether the drug is an NME or a reformulation of a known drug substance, the nature of the safety findings from the clinical trials, and the nonclinical data for the drug under development. For the safety evaluation of an NME intended for treatment of chronic pain, we recommend sponsors refer to 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 for drugs intended for long-term treatment of non-life-threatening conditions and to the guidance for industry Premarketing Risk Assessment. These guidances make recommendations on the minimum size of the database. These minimums also should apply to a proposed new chronic indication for a drug previously approved for an acute indication only. A safety database larger than recommended in these guidances may be warranted for a number of reasons (many of which are discussed in these guidances), including safety signals emerging as more clinical data become available.

For reformulations of drugs with existing chronic pain indications, the size of the safety database should reflect the differences from existing formulations of the drug and the gap in safety data expected from these differences. For example, an oral drug indicated for chronic pain might be reformulated into a transdermal formulation. In general, in the case of reformulated drugs, the amount of safety data that should be collected to support safe use depends on differences in pharmacokinetics, particularly if the new formulation resulted in a drug with a delayed $C_{\text{max}}$ and a prolonged half-life. To determine an appropriate number of subjects for the safety database for a drug previously approved for a nonanalgesic 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.

As efficacy trials for acute indications are sometimes limited in duration by the clinical setting under study, efforts should be made to ensure an adequate collection of safety data over a duration of use that can be reasonably expected in the intended patient population. For example, when evaluating an oral analgesic in the setting of postoperative pain, whereas efficacy endpoints may be on Day 1 or 2, safety assessments should be collected for as long as subjects can potentially benefit from the drug. Consideration should be given to obtaining safety data from additional trials if it is likely that the drug can be used for days to weeks.
c. Class-related safety concerns

Safety monitoring should address drug class-related concerns for new drug substances in existing analgesic drug classes. Clinical trials for development of opioids or other new drug substances that are capable of CNS depression should include monitoring of oxygen saturation and vital signs at appropriately frequent intervals.

Drugs with effects on the CNS should be evaluated for their abuse liability as a part of their development, because they may require scheduling under the Controlled Substances Act. Because this evaluation can alter what types of data need to be collected in the clinical trials, sponsors are strongly encouraged to discuss their plans for this assessment with the FDA early in development. For example, subjects receiving new drug substances with effects on the CNS should be evaluated for the development of tolerance and signs of drug withdrawal syndromes.

All extended-release and long-acting (ER/LA) opioid analgesic drug products and transmucosal immediate-release fentanyl products currently have a risk evaluation and mitigation strategy (REMS). We intend to require a REMS for other analgesic drug products with similar risks when the statutory criteria for requiring a REMS are met.

In addition, we strongly recommend that drug products with the potential for abuse, particularly ER/LA opioid analgesic drugs, be formulated with abuse-deterrent properties. Refer to the draft guidance for industry Abuse-Deterrent Opioids — Evaluation and Labeling for guidance pertaining to the evaluation of abuse-deterrent opioids.

All ER/LA opioid analgesic drugs with NDAs approved as of the date of this guidance also are required to conduct five postmarketing study requirements (PMRs) to further evaluate the risk of misuse, abuse, addiction, hyperalgesia, overdose, and death. The first four of these PMRs are:

1. Studies to provide quantitative estimates of the serious risks of misuse, abuse, addiction, overdose, and death associated with long-term use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid drugs

2. Studies to develop and validate measures of the following opioid-related adverse events: misuse, abuse, addiction, overdose, and death

3. A study to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify misuse, abuse, addiction, overdose, and death in any existing postmarketing databases to be employed in these studies

4. A study to define and validate “doctor/pharmacy shopping” as outcomes suggestive of misuse, abuse, and/or addiction

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14 See the draft guidance for industry Assessment of Abuse Potential of Drugs. When final, this guidance will represent the FDA’s current thinking on this topic.

15 When final, this guidance will represent the FDA’s current thinking on this topic.
The fifth PMR is a clinical trial to estimate the serious risk of the development of hyperalgesia following use of ER/LA opioid analgesics for at least 1 year to treat chronic pain with a suggested assessment of the development of tolerance following use of ER/LA opioid analgesics.

We anticipate requiring sponsors of most ER/LA opioid analgesic drugs that are the subject of new applications to conduct these PMRs, given the similar risk profile of the ER/LA opioid class. However, in some cases, the type of trial described in the fifth PMR may need to be conducted before approval, depending on the particular overall risk-benefit assessment of the drug under review. We encourage the sponsor to discuss this possibility with the division as early as possible.

Sponsors of all new NSAIDs should discuss with the review division as early as possible the need for trials to assess cardiovascular risk for thromboembolic events including myocardial infarction, sudden cardiac death, and cerebrovascular accident. Safety monitoring for this trial type should include a data monitoring committee with prespecified plans for adjudication of all pertinent events. It is also important to record adequate information to understand the potential effects of the drug on blood pressure, the occurrence of congestive heart failure, peripheral edema, renal function, gastrointestinal toxicity (e.g., perforations, obstructions, bleeds), and liver function during all clinical trials for these drugs.

d. New routes of administration

New routes of administration may raise potential route-related safety concerns. Information should be collected as appropriate for the route of administration. Topical products can be intended for local drug delivery or can be intended to provide transdermal systemic drug delivery. For these products it is important to include an assessment of dermal toxicity. This should include cumulative irritancy studies, allergenicity (contact allergy) studies, and phototoxicity and photallergenicity (photo contact allergy) studies (see section IV.C.2., Skin Studies for Topical Products). It is also important to examine the effects of heat on the delivery of drug from topical products, both external heat and the effects of exercise. For products intended to deliver the drug to local tissue, with anticipated limited systemic toxicity, it is also important to study a maximal exposure situation. As one example, for a topical NSAID cream intended to treat arthritis pain, maximal exposure can be evaluated after application to two knees and two hands. In addition, residual drug in patch formulations may place household contacts at risk for accidental exposure. Specific methods for safe disposal should be developed to minimize this risk.

Studies of drugs administered by the intranasal route of administration should include data from visual inspections of mucous membranes. Studies of drugs by inhalational route of administration should include thorough pulmonary safety assessments, including, at a minimum, pulmonary function testing. Spray pattern and droplet size should be characterized for all inhalational and intranasal drugs early in development.
New routes of administration for approved drugs (e.g., pulmonary administration of a drug approved previously for oral use) should include appropriate nonclinical bridging studies focusing on the toxicities specific to the new route.

**B. Specific Efficacy Trial Considerations**

1. Trial Design

All analgesics have characteristics that create a challenge for clinical trial design. Pain is a subjective phenomenon. Pain often fluctuates over time. For example, acute pain in the postoperative period typically decreases over days; chronic pain of osteoarthritis can wax and wane over weeks. In addition, it is common to see a fairly substantial placebo effect in analgesic trials. There are known instances of failed clinical trials of analgesic drugs later found to be effective. As a result, noninferiority designs cannot provide definitive evidence of efficacy in analgesic trials. In an analgesic trial, if there is no difference between two active treatment groups, it may be because both treatments are successful in managing pain or because neither treatment was successful in managing pain. Another way to describe this is that the trial lacked assay sensitivity. Therefore, trials intended to support a finding of efficacy for an analgesic should be designed as superiority trials. The comparator can be a lower dose of the investigational drug, a placebo, or an active comparator.

One of the most difficult challenges for a superiority trial of an analgesic is high dropout rates, particularly in 12-week trials intended to support efficacy for a chronic pain indication. The pattern of these early discontinuations generally is not random. Subjects are more likely to drop out because of an adverse event from an active treatment arm, whereas subjects in a placebo or dose-control treatment arm are more likely to drop out because of a lack of efficacy. This nonrandom dropout pattern poses special concerns for managing missing data during the analysis of efficacy; therefore, efforts should be made to minimize dropouts to a greater degree. There are a number of approaches that can be used to help reduce dropout rates. (See section IV.B.11., Statistical Considerations.)

a. Use of rescue medication

One way to minimize dropouts from lack of efficacy is to provide rescue medication. This can be done in a manner that does not interfere with pain assessments. For example, pain can be assessed just before the administration of rescue medication and these data carried over to the next scheduled assessment time. Alternatively, rescue medication can be limited so that none is permitted within a prespecified time before a pain assessment.

b. Add-on design

Another option to consider is an add-on design where subjects are permitted to continue with their prior analgesic regimen and an investigational drug or placebo are added on to the existing therapy. However, it is important to note that an add-on design may only support an adjunctive treatment indication if the drug has not otherwise been well studied in the setting of nonconcomitant use.
c. Adequate period of drug titration

Too rapid a titration can result in poor tolerability for many analgesics, particularly opioids. A slow titration may decrease side effects and ensure that important safety signs and symptoms are detected before they become dangerous. Starting an opioid at a relatively high dose can result in nausea, vomiting, excessive sedation, or respiratory depression. Even with a slow titration, not all subjects assigned to a particular analgesic dose may tolerate the prespecified dose, particularly with opioids.

d. Titrate-to-effect design

Although many analgesics can be studied in a fixed-dose, parallel-arm design, others may need to be studied in a titrate-to-effect design to improve subject retention and to provide a more realistic picture of efficacy and safety. The drawback of a titrate-to-effect design can be failure to accurately identify the dose response, because different prespecified doses across treatment groups are not available for comparison. Consideration should be given to evaluating the dose response within individuals when subjects are titrated to an effective dose, or in separate, dedicated pharmacodynamic studies.

e. Enrichment design

An enrichment design can be useful for decreasing early dropouts caused by adverse events. One type of enrichment design titrates both active and placebo groups to a tolerable dose based on prespecified criteria. Another approach is to titrate all subjects on active investigational drug to a dose that is both tolerable and meets prespecified efficacy criteria such as a percent reduction in pain intensity from the baseline pain intensity score. Only those subjects who can be successfully titrated using prespecified criteria, such as a percent reduction in pain intensity from the baseline pain intensity score with no intolerable adverse events, are continued in the trial. Subjects are then randomized to remain on investigational drug or to placebo. If the drug under study is an opioid or another drug that cannot be discontinued abruptly, there should be an adequate blinded taper following randomization so that subjects randomized to placebo do not undergo either a clinically obvious or a more subtle withdrawal syndrome. Because opioid withdrawal can be associated with pain, rather than using time to return of pain as the endpoint, pain intensity can be compared at the end of a 12-week period. An enrichment design may be particularly well suited for the demonstration of efficacy for a reformulation of an established analgesic.

2. Single-Dose Characteristics

To fully characterize the efficacy of an analgesic, we recommend evaluating single-dose characteristics including changes in pain intensity assessments following one dose, time to onset of pain relief, and time to rescue or re-medication. Whereas a specific single-dose trial can accomplish this goal, these characterizations can be assessed around the first dose in a multiple-dose trial. Onset of effect has most commonly been evaluated using two stopwatches. To avoid overestimating a placebo effect, as can occur with the use of just a single stopwatch measured
endpoint, sponsors are encouraged to measure both time to onset of detectable pain relief and to
meaningful pain relief. Repeated measures of pain intensity and pain relief over the trial period
should establish the time of maximal effect of the drug. The duration of analgesia generally is
defined by the median time to a request for rescue or re-medication. It is important that onset of
analgesia, duration of effect, and magnitude of effect be determined in clinically relevant patient
populations.

3. Multiple-Dose Data

Unless the drug under study is intended for single-dose use, multiple-dose trials should be
carried out to confirm efficacy over time.

a. Acute pain

In many acute pain settings, pain intensity changes over a relatively short period of time, which
may present challenges in designing a trial. Nevertheless, it is important to explore the
appropriate use of a drug during a multiple-dose period. For parenteral drugs for use in the
postoperative period, the primary efficacy period should be no less than 24 hours for one trial
and 48 hours for the second trial when a second trial is needed, but longer periods of time also
may be appropriate and are encouraged when feasible. However, we strongly encourage the trial
duration to extend for as long as it is suitable for subjects to remain on the parenteral therapy to
obtain additional efficacy and safety information.

For oral analgesics, longer efficacy studies are encouraged. We recommend confirming an
appropriate dosing interval during multiple-dose treatment, taking into consideration
pharmacokinetic characteristics and the duration of effect determined during earlier trials.
Important considerations to include in designing these trials are the magnitude of effect and the
effects of rescue medication use on re-dosing and efficacy outcome measures. To avoid
interference in efficacy measures at scheduled times because of the use of rescue medication,
sponsors can make pain assessments before rescue, asking subjects to report the pain intensity at
the current time with no recall period, and imputed to the following scheduled assessment time.
The primary efficacy endpoint can be based on a time-weighted analysis over the trial period.

Analgesics considered appropriate for the management of acute pain are often used on a chronic,
intermittent basis. To understand the durability of efficacy in this setting, and perhaps more
importantly, the safety of this type of use, we recommend studying such drugs under these
conditions of use. An important question to consider is whether efficacy is sustained with
chronic, intermittent use, particularly when around-the-clock dosing is no longer necessary. One
approach to this evaluation is to permit subjects to use the analgesic on an as-needed basis
following a multiple-dose, around-the-clock trial period. An additional efficacy analysis can
then be performed to determine whether the drug continues to provide a reduction in pain.

b. Chronic pain

Consistent with studies of many drugs intended for chronic administration for other indications,
we recommend at least a 3-month duration for studies evaluating analgesia in chronic pain. A
shorter trial duration can be considered in situations that are not suitable for a full 3-month trial because of clinical constraints (e.g., terminal cancer pain). It is important that the efficacy outcome include pain assessments throughout the trial and also at the end of the trial. The recall period should be specified as well as the pain concept sought. For example, the subjects can be asked to rate the worst pain over a 24-hour recall period. Such assessments ensure that analgesics in this chronic use setting can be evaluated for the presence of consistent and durable efficacy. The primary efficacy endpoint should be evaluated as a change in pain intensity from baseline to the end of the double-blind period of the trial. An analysis of the pain intensity as a time-weighted analysis can be highly informative and is recommended as a secondary endpoint.

Demonstrating efficacy in a 12-week trial of chronic pain with an opioid analgesic can be challenging. Relatively high rates of early discontinuations, often caused by adverse events, can lead to great difficulty in evaluating missing data. All imputation methods offer strengths and weaknesses that can affect the results. Opioids typically are titrated to an effective dose in clinical practice and have no ceiling effect for analgesia. Therefore, an upper limit for the dosing range need not be identified. As previously discussed, clinical trials of opioids, particularly opioid reformulations, may be particularly well suited for a titrate-to-effect design. In this trial type, subjects are titrated to an effective and tolerable dose. This can be done as an open-label titration followed by randomization to active or placebo treatment groups for subjects who meet criteria for successful titration. Another option is to randomize subjects and then titrate to an effective and tolerable dose.

Analgesics that belong to a drug class with a well-defined ceiling effect for efficacy and a dosing range that encompasses only a limited number of doses may be better suited for clinical trials with a parallel, fixed-dose design. This design type provides an opportunity to establish a dose response across doses and, for new drugs, identify the top of the dosing range. NSAIDs are an example of a drug class that has been studied successfully with this design. In contrast to opioids, NSAIDs generally result in fewer bothersome adverse events such as nausea and sedation after dosing has been initiated, so high dropout rates are less common in 12-week trials. However, for approved analgesics with an identified dosing range and a known dose-response relationship for side effect tolerability, when a new analgesic indication is sought, a titrate-to-effect design may be acceptable. This depends on the similarities of the new patient population as compared to the patient population associated with the existing indication. If the populations differ substantially in age, comorbidities, or concomitant medications, a safe and effective dosing range may need to be established for the new indication. Parallel-arm, fixed-dose trials should be considered for the purpose of establishing evidence of a dose response to support the proposed doses.

NMEs should be adequately explored in phase 2 to determine the best approach to trial design in phase 3. An end-of-phase 2 meeting is strongly advised so that the division can provide input on that approach.

4. **Trial Population**

We encourage sponsors to apply the following principles to subject selection in analgesic clinical trials. Patient populations in phase 3 clinical trials should represent as much as possible those
patients reasonably expected to use the drug after it is marketed. This is particularly important for drugs that may have general pain claims. As a general rule, the characteristics of the population should not be unnecessarily restrictive. In some clinical development programs, it may be useful for one phase 3 clinical trial to have entry criteria that are more narrowly defined, allowing for enrichment where appropriate, while a second clinical trial for the same indication may have broader entry criteria, the results of which can help address generalizability.

Although efficacy should be replicated in typical drug development programs, we strongly encourage sponsors to avoid conducting two identical trials of the same population as the sole support for efficacy, particularly with NMEs. It is critical that a variety of clinical situations where the drug may be effective and useful be adequately explored. This is particularly important for NMEs. We encourage sponsors to evaluate a broad range of pain populations for NMEs that are the first in a new class of analgesics. Trial populations should include subjects with nociceptive somatic and visceral pain and neuropathic pain conditions to enable demonstration of the most appropriate populations for inclusion in the drug’s indication.

In situations when pain is a manifestation of systemic disease, it may be important to quantify in the protocol the extent and severity of the underlying systemic disease at the start of the clinical trial. It is also important to ensure that all clinical trial subjects have access to appropriate care for the underlying disease throughout the course of the clinical trial. When feasible, attempts should be made to keep treatment of the underlying disease stable during clinical trials. When changes to the subject’s medical treatment outside of the trial become necessary, it is important to record the reasons underlying those changes on the case report form.

For all analgesic efficacy trials, the size of the enrollment should be based on the number of subjects needed to demonstrate a meaningful difference in treatment arms and should not be so large as to give statistical significance to a difference in effect size that is too small to have clinical relevance. This consideration should be addressed in the powering discussion of the statistical plan.

5. **Entry Criteria**

The inclusion and exclusion criteria should describe characteristics of the trial population that support its ability to provide appropriate data for the proposed indication.

Some criteria are important to assess when designing analgesic efficacy trials. One criterion is whether individuals with a prior history of substance abuse can be included in the trial. If this is to be permitted, specific monitoring of substance abuse or misuse should be incorporated into the trial. Another criterion is whether individuals are involved in activities that can provide secondary gain that may interfere with assessments. Defining a population as refractory to other analgesic treatments or as opioid tolerant are other criteria that may be important to consider.

We recommend sponsors give consideration to the role of ongoing concomitant medications for the management of pain in analgesic clinical trials. The following general principles should be considered:
• Clinical pharmacology trials may be needed to characterize the pharmacokinetic and/or pharmacodynamic interactions between the investigational drug and likely concomitant medication before these drugs are co-administered in later-phase clinical trials.

• Trials in which subjects continue treatment with their previous analgesic medication may provide information about the investigational drug as adjunctive therapy and, therefore, support an indication for use as an adjunctive treatment for pain.

• Trials in which subjects are to continue receiving a prespecified variety of generally accepted therapies for the underlying pain condition can have certain strengths (e.g., they can mimic the actual use of the drug after it is marketed). However, they risk an imbalance of concomitant medications across treatment groups. It is important to consider whether stratification for concomitant medications may be useful as part of the analysis plan with this design type.

• It is important to consider the use of nondrug therapies (e.g., physical therapy, transcutaneous electrical nerve stimulation units, and alternative treatment approaches such as acupuncture) in the inclusion and exclusion criteria. If permitted, the treatment regimen should remain stable for a period of time before the trial and remain unchanged throughout the trial period.

6. Randomization, Stratification, and Blinding

Randomization ensures balance between arms on important prognostic factors, whether measured or not. It is important to document the method of randomization in the protocol and the outcome of randomization in the final report. Stratification, adaptive allocation, or other schemes to reduce variance between arms can be used as needed. If employed, we recommend that a discussion of how the analyses will account for such schemes be included in the protocol.

There are a few important considerations for randomization, stratification, and blinding specific to analgesic trials. Stratification can be considered for important baseline characteristics or concomitant medications. As noted earlier, analgesics such as opioids that have known withdrawal syndromes are not suitable for randomized withdrawal designs that do not incorporate an adequate period to taper the drug. The outcome measures for analgesic trials are subjective assessments. Therefore, a double-blind design is highly desirable to reduce bias in the measurement of efficacy outcome measures. Consideration should be given to assessing the success of blinding in the trials (e.g., asking subjects at the end of treatment which assignment they believe they received).

7. Specific Populations

The usual assessments of specific populations appropriately apply to analgesic development. However, pediatric pain is considered an unmet medical need because few analgesics carry pediatric indications or specific pediatric dosing recommendations based on clinical data. The suitability of pediatric studies should be considered early in development. Sponsors are encouraged to begin discussions about their pediatric clinical development plan early in
contains nonbinding recommendations

draft — not for implementation

872 development because applicants submitting NDAs (or supplements) for a new active ingredient,
new indication, new dosage form, new dosing regimen, or new route of administration of a
drug\textsuperscript{16} are required to submit pediatric study plans no later than 60 days after an end-of-phase 2
meeting, unless another time has been separately agreed upon.\textsuperscript{17} For further information about
required pediatric studies, we recommend sponsors refer to the Pediatric Research Equity Act\textsuperscript{18}
as amended by the Food and Drug Administration Safety and Innovation Act.\textsuperscript{19}

- **Establishing indications for NMEs, or for a class of drugs not listed below**

For NMEs of either a new drug class or a class of drugs that is still establishing its safety and
efficacy profile for analgesia in adults (such as the serotonin/norepinephrine reuptake inhibitor
class), full efficacy, safety, and pharmacokinetic studies should be conducted in the full age
range of pediatric subjects.

- **Establishing pediatric indications for NMEs and reformulations of approved drugs**

When establishing a pediatric pain indication for these drug types, extrapolation of adult efficacy
data down to the age of 2 years may be appropriate provided: (1) the drug’s mechanism of
action is known; (2) this mechanism is similar in the pediatric and adult populations; (3) the
metabolic pathway is established and is similar between adult and pediatric populations; and (4)
the condition(s) being treated are considered similar in adults and children. Drug classes that fit
into this category and thus generally would allow for the extrapolation of adult efficacy data
down to the age of 2 years include the opioids, nonsteroidal anti-inflammatory agents, local
anesthetics, and acetaminophen. Pharmacokinetic studies and safety data should be obtained to
conclusively permit the extrapolation of adult data to this population.

For pediatric subjects under the age of 2 years, full efficacy, safety, and pharmacokinetic studies
should be conducted. However, we would be willing to consider alternative study designs such
as add-on studies where an endpoint could be a reduction in amount of rescue medication needed
or a decrease in the need for caregiver- or nurse-controlled analgesia so long as the study design
would allow for the determination that the drug was exerting an analgesic effect using a well-
defined and reliable observation-based measure of signs thought to be related to pain in the target
patient population and context of use (e.g., crying, arching back).

8. **Dose Selection**

Dose selection for analgesic trials should take into consideration the nature of the drug and likely
concomitant medications. For CNS depressants, concomitant use of other CNS depressants
should be minimized in early trials and explored cautiously later, if such use is expected in the
clinical setting. Protocols should include an adequate titration period with monitoring for CNS

\textsuperscript{16}See section 505(B)(a)(1) of the FD&C Act.

\textsuperscript{17}See section 505B(e)(2)(A) of the FD&C Act.

\textsuperscript{18}See Public Law 108-155 (2003).

\textsuperscript{19}See Public Law 112-144 (2012).
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912 depression. NMEs should be evaluated for possible withdrawal syndromes, and whether known or expected, adequate tapering periods should be incorporated at the end of the trial. In NSAID trials, sponsors should consider dosing with respect to renal function.

916 9. Choice of Comparators

917 As previously noted, efficacy trials for analgesics should be superiority trials. The comparator can be placebo, a lower dose of the investigational drug, or an approved drug if the investigational drug can be expected to be superior. For an approved drug, consideration can be given to a trial design with a dose control as comparator (i.e., a dose lower than known to offer full efficacy). Care should be taken to avoid drawing comparative claims about superiority to an approved drug if the dosing of the approved comparator drug was at or below the lower range of effective dosing.

926 Even if a placebo-controlled design is used, sponsors are encouraged to include an active comparator in single-dose as well as multiple-dose trials. An active comparator may provide useful information on the relative utility of the investigational drug in that population, particularly when there is already an analgesic that is commonly used for the type of pain under evaluation. An active comparator also can provide additional information on assay sensitivity in a given trial, which can be helpful in distinguishing a trial that doesn’t show a difference because of a lack of efficacy from one that failed because of problems with the design.

934 10. Efficacy Endpoints

935 There is a broad spectrum of information that should be collected to understand the effects of an analgesic drug and to adequately inform the prescriber. In general, the outcome measures for acute pain and chronic pain studies are similar. When selecting instruments to measure study outcomes, it is important to take into consideration whether the trial population is representative of the population in which the instrument was developed and its measurement properties were demonstrated. It is also important that instruments be sensitive to change over the time period of the trial.

944 a. Pain intensity

946 Pain intensity is the fundamental measure that defines the efficacy of an analgesic drug. There are no objective measures for pain intensity. As PROs, pain intensity can be measured by numerical rating scales, visual analog scales, or categorical scales. Each of these measurement techniques has advantages and disadvantages that should be considered in the design. It is important also to choose the endpoint measure appropriate to the patient population and clinical situation being studied. When disease-specific pain measures are available, they may be preferable to nonspecific measures if adequately developed because they may be more sensitive to change and more interpretable.
b. Function

Patients often experience some negative effects of pain on aspects of physical function or emotional function, particularly with chronic pain. In addition, drug-related adverse events can affect function. It is important to collect information on the effects of treatment on function, particularly for chronic pain indications, to fully inform the risk-benefit assessment. We encourage the use of existing well-defined and reliable scales specifically developed and tested in the patient population under evaluation, sensitive enough to detect a deficit, and responsive enough to detect a clinically meaningful change over time. We also encourage efforts to develop new well-defined and reliable instruments where necessary.20,21

c. Health-related quality of life

Health-related quality of life (HRQL) is a multidomain concept that represents the subject’s overall perception of the effect of an illness and its treatment. An HRQL measure captures, at a minimum, physical, psychological (including emotional and cognitive), and social functioning. In general, HRQL instruments are not appropriate as primary endpoints for several reasons: (1) some HRQL instruments include inappropriate items for drug development trials (e.g., financial well-being); (2) concepts and domains measured are distal to the effect of treatment; (3) the proximal effects of treatment on how subjects feel and function may not be captured (e.g., items reflecting personal well-being may be too far downstream to reflect treatment benefit); and (4) they reflect or respond to other causal factors that increase variability of the measurement and impair the interpretation of treatment effect.

The inclusion of distal attributes of well-being that typify HRQL questionnaires attenuate the overall ability of the measure to detect change. This occurs even when improvements in personal well-being items more securely reflect treatment benefits. Even expected improvements in personal relationships or social participation can be less likely to show change across the duration of the clinical trial. A claim based on HRQL measurement to demonstrate investigational treatment benefit can be misleading if treatment adverse effects are not yet fully known and the HRQL instrument does not prospectively measure the effect of relevant adverse effects on HRQL. Overall, HRQL is inappropriate as a primary endpoint, likely challenging as a secondary endpoint, but certainly welcome as an exploratory endpoint when an instrument addresses concepts about which subjects express concern.

d. Rescue medication

In studies where rescue medications are allowed, it is critical to record, quantify, and analyze rescue medication use. The protocol should identify what type and amount of rescue medication will be acceptable during the study. Changes in pain intensity and pain relief measures cannot be meaningfully interpreted in the absence of information on rescue medication use. In the absence of rescue medication information, adverse event rates also can be misinterpreted. In general, it is

20 See the guidance for industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.

21 See note 6, supra.
important that protocols specify the drug or drugs permitted as the rescue medication. It is also
important that the protocol specify at what level of pain, based on the scales or other assessments
used to measure pain intensity, rescue medication can or should be administered, and the timing
of pain measurements in relation to allowed rescue medication use.

   e. Global single-item assessment

General single-item assessments cannot be considered well-defined and reliable and are not
recommended for use to support claims of treatment benefit. Global assessments generally are
measured by single questions that use a categorical or visual analog scale for scoring overall
response to treatment or status of the subject. Global assessments aim to elucidate the subject’s
integrated, overall experience with the analgesic, rather than an additional assessment of efficacy
or safety. They are sometimes used as exploratory endpoints to use when interpreting change
using other measures. It is impossible to identify one specific question that best captures a
subject’s experience in all circumstances and for all purposes. Although useful as a means of
broadly assessing the subject status and helping to integrate the effects of drug efficacy and
safety from the perspective of the subject, the interpretation of the question and resulting
response will differ from one subject to the next. However, global assessments may be useful for
providing context for understanding the efficacy and safety findings.

   f. Opioid sparing

Opioid sparing resulting from the use of a nonopioid therapy can be considered an outcome
measure in some chronic pain states or pain processes. It can provide evidence of analgesic
efficacy in a manner similar to the assessment of amount of rescue medication use. However, for
drugs intended only for concomitant use with opioids, a reduction in opioid use alone may not
have clinical significance unless additional benefit can be demonstrated, such as fewer opioid-
related adverse events.

   g. Sleep

We encourage attempts to evaluate effects of analgesics on sleep, but such attempts may not be
appropriate to support a specific sleep-related claim unless found to provide a clinically and
statistically additional benefit to the analgesic effect. A single-item general assessment of a
complex multidomain concept such as sleep quality cannot be considered well-defined and
reliable to support a claim. Sleep disorders include difficulty falling asleep, staying asleep, and
waking up refreshed. We encourage using well-defined and reliable methods for measuring the
effects of analgesics on sleep. It is important to also consider the use of indirect assessments of
sleep using clinic-based tests (e.g., polysomnography) if sleep-related claims are being sought.

   h. Additional measures

Other well-defined and reliable PRO measures also can be incorporated into analgesic drug trials
and can, if used in an appropriately designed trial, serve as the basis of a labeling claim.
Sponsors are encouraged to discuss plans to use such additional outcomes with the division.
11. Statistical Considerations

The statistical analysis of analgesic trials has two related but distinct goals. First, it should be demonstrated, at an acceptable level of confidence, that the investigational drug has a beneficial effect. Second, it is important to describe the drug’s efficacy in some detail.

The first goal normally should be addressed by significance testing, which controls the probability of falsely finding that an ineffective drug is effective. As the probability of such false findings is multiplied when there are multiple tests, it is important to specify in advance a single, primary analysis without whose success the trial will not be claimed to provide evidence of efficacy.

There should be a multidimensional description of the drug’s efficacy. Questions to be answered can include: How large were the effects? How did the effects vary from subject to subject? How soon after dosing did the effects appear, and how long did efficacy last? The answers to these questions will certainly involve measurements at multiple time points, and they may involve different kinds of measurements as well.

a. Demonstrating efficacy

It is important to choose a single, clinically relevant statistical test that is expected to reliably distinguish the experimental drug from the control. This distinction is likely to be based on a visual or numerical rating of pain intensity, or a categorical rating with several categories. It may be a single rating at a given point in time, or an average or other summary of several ratings over a period of time. For chronic conditions, however, the outcomes at the end of the trial are of special interest, as they may be the best indicators of benefit in the longer term.

A responder analysis, in which the outcome for each subject is summarized as a success or a failure based on a single cut-off point (e.g., 30 percent reduction in pain (with early discontinuation counted as a failure)), can be used. As discussed below, such analyses are easy for clinicians to interpret, and they can greatly mitigate the problems of missing data. There may be a substantial loss of information, however, when detailed observations on each subject are reduced to a single dichotomy. Therefore, this form of a responder analysis may not be the most powerful method of demonstrating a beneficial effect. However, a responder analysis that evaluates responder status across the full range of outcomes for an endpoint can be helpful in describing the effects of the experimental treatment. Sponsors are encouraged to include a presentation of these analyses in the package insert to better inform prescribers of the trial outcome. The percent of subjects, \( y \), achieving a reduction in pain of \( x \) percent, for \( x \) ranging from 0 to 100, can be plotted against \( y^* \) (cumulative distribution function).

The primary test for a numerical or even a categorical score can be based on a mean across subjects. This is not because the average of different subjects’ pain scores is itself a meaningful quantity, as it may not be. Rather, it provides a valid, sensitive test for systematic differences between groups in individual scores. For the sample sizes likely to be needed in analgesic trials, the two-sample t-test is robust against departures from normality and therefore can be considered essentially nonparametric. Rank-based nonparametric methods also may be appropriate. Again,
however, it is important to choose the method in advance to avoid the problems associated with multiplicity. Protocols that specify alternative methods as needed are troublesome, because there may not be agreement on whether or not they are needed. We recommend specifying in the protocol a single, sufficiently robust method, whether rank-based or nominally parametric.

b. Descriptive statistics

We recommend sponsors provide detailed descriptions of the clinically relevant effects of the analgesic drug. The time course of effects is particularly important because it will inform health care providers on the range of dosing intervals that may be useful. It will, therefore, often be useful to report measures of pain at multiple time points by descriptive statistics (i.e., inferential statistics beyond those for primary efficacy variables generally are not appropriate for inclusion in labeling). The need for such a detailed, multifaceted description of effects is not in conflict with the need for a single, primary analysis to demonstrate that the drug has an effect.

It is important for descriptive analyses to represent the variability from subject to subject. Plots of cumulative distributions, boxplots, or standard deviations can be useful for this purpose. P-values, or even confidence intervals or standard errors, are not useful in portraying individual variability; rather, they are measures of the uncertainty in mean values. We recommend including descriptive statistics if they are useful and credible, not just if they are statistically significant.

c. Missing data

It is important that every appropriate means be taken to minimize dropouts. However, we acknowledge that treatment discontinuations are inevitable in analgesic trials.

It is a common finding in some analgesic drug classes that subjects dropping out from the placebo group and active treatment group differ with respect to reason for early discontinuation. Early discontinuations because of a lack of efficacy often are more prevalent in the placebo group, whereas early discontinuations because of adverse events often are more prevalent in the active treatment group. Thus, even when the treatment groups are balanced at baseline by randomization, they no longer comprise comparable subjects at the end of the trial. Each group has remaining whatever subjects did not experience intolerable side effects or lack of efficacy, and this subset of subjects is systematically different for different treatments. For this reason, comparison of completers only is not useful as a primary analysis.

In general, it is important that bad outcomes be attributed to subjects who were unable to complete the course of treatment because such subjects did not benefit from the treatment. This attribution is often misunderstood as a matter of estimation, but there is in a sense nothing to estimate. The missing outcomes are not merely unobserved, they are nonexistent.

In the past, bad outcomes on analgesic trials were assigned by a single imputation strategy such as last observation carried forward (LOCF). The use of a LOCF strategy in multiple-dose trials, however, might result in good pain scores being carried forward for subjects who experienced relief of pain before dropping out because of excessive toxicity (e.g., a potentially excessive...
dose). The LOCF method in such a case would assign misleading, good outcomes to such subjects. In contrast, the baseline observation carried forward method would appear to have some pragmatic justification because a bad outcome would be assigned to all subjects dropping out. However, the method would not reflect the statistical uncertainty or variability about the imputation and could consequently lead to inaccurate inferences. This is true of all single-imputation strategies. Therefore, we do not recommend their use in multiple-dose, chronic pain trials.

We recommend some other method be used to avoid attributing an overall benefit to a drug that does not benefit individual subjects. Possible methods may include model-based approaches that address the specific needs of analgesic trials. The model should be specified and the assumptions underlying the model should be justified. Another possible strategy may be to use a composite outcome that incorporates dropout in the definition of a responder (see the responder analysis described in section IV.B.11.a., Demonstrating efficacy). Regardless of the technique used to handle missing data, sensitivity analyses should be performed to assess the effects of the analytic method on the results.

Finally, because the analytic strategy to handle missing data for the primary efficacy evaluation is critically important, that choice should be prespecified before the blind is broken. Preferably, the statistical analysis plan should be finalized before trial initiation.

d. Covariates

Randomized studies can be analyzed by straightforward methods without covariates (e.g., chi-square tests for binary outcomes and t-tests or rank tests for numerical outcomes). Randomization and significance testing control the probability of a chance imbalance producing a false positive result for an ineffective drug.

However, methods using covariates may reduce the variability in the estimated treatment effects, leading to more powerful tests. We recommend choosing covariates in advance on the basis of their anticipated ability to account for variability in the outcome measure. Post hoc adjustment for imbalances is neither necessary nor desirable, and likely will raise concerns about multiplicity. In any case, we recommend that variables that may be affected by treatment not be considered as covariates.

e. Bivariate outcomes

As previously discussed, rescue medication is usually available in opioid analgesic trials. The interpretation of the results is complicated by this practice. If one group of subjects had less pain but more use of rescue medication than another, it may not be clear which treatment was better. We recommend that the protocol specify a way of dealing jointly with pain and rescue. This can be done in various ways.

A binary outcome can be defined for each individual subject, as discussed in the following section. The subject should be considered successfully treated if he or she reports a pain score
less than some prespecified value and takes less than a prespecified amount of rescue medication. Analysis then proceeds as for any other binary outcome.

By extension, a single numerical score can be assigned to each subject, based on both pain and rescue medication. It is difficult to define an optimal way of combining these data, but as long as a method is prespecified, it does not need to be optimal. Any combination of outcomes indicating improved pain or less rescue use, without a worsening of the other, likely would show efficacy of the investigational drug (see section IV.B.10.f., Opioid sparing).

Alternatively, multivariate methods can be applied to the aggregate outcomes for pain and for rescue medication. Again, the choice of such methods need not be shown to be optimal, as long as it is made in advance and is reasonable.

f. Responder analyses

For some drugs, comparing the change in the mean scores of treatment groups may not be the best analysis for efficacy. An alternate approach is to compare the number of subjects reaching prespecified criteria for success (e.g., completing the trial along with showing a certain reduction in their pain intensity). It is important that a responder analysis incorporate a criterion of improvement in pain along with criteria for use of rescue medication and other outcome measures. Sponsors are encouraged to explore the behavior of a variety of outcome measures and responder definitions during phase 2 to provide a rationale for use of a responder analysis as primary analysis in phase 3 trials.

g. Multiplicity

As previously mentioned, in addition to the primary assessment of pain intensity and relief, other assessments of pain and its effect on subjects may be important in fully elucidating the risk-benefit relationship for the drug. The overall probability of a false positive finding for a completely ineffective drug is controlled by specifying a single primary analysis. However, if secondary analyses are intended to support important labeling claims, we recommend considering the probability of errors in these secondary analyses. We also recommend laying out a plan in the protocol for controlling them.

C. Other Considerations

1. Risk Management Considerations

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) grants the FDA the authority to require a REMS for certain drug products, if we determine that such a strategy is

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22 Section 505-1 applies to applications for approval of prescription drugs submitted under FD&C Act subsections 505(b) or (j) and applications submitted under section 351 of the Public Health Service Act. These applications are termed covered applications and refer to NDAs, abbreviated new drug applications, and biologics license applications.
necessary to ensure that the benefits of the drug outweigh the risks.\textsuperscript{23} We may determine that a REMS is necessary to support approval of a drug application or may require a REMS after a drug is approved, on the basis of new safety information.\textsuperscript{24}

We view drug risk management as an iterative process encompassing the assessment of a drug’s risks and benefits, and developing and implementing tools to minimize the risks while preserving the drug’s benefits. It is important in developing any REMS to begin by defining the serious risks specific to the drug that must be managed. For example, we have determined that a REMS is required for ER/LA opioid analgesics to mitigate the serious risks of overdose, abuse, and addiction.

We encourage sponsors to discuss the potential need for a REMS for their analgesic drugs with the division as early as possible during the clinical development program. If we advise a sponsor that a REMS is required, the proposed REMS should be complete at the time of submission of the application. Sponsors should refer to the draft guidance for industry Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications for information on how to format and submit a proposed REMS to the FDA.\textsuperscript{25}

2. Skin Studies for Topical Products

Topical products, either those intended for local drug delivery or those intended to provide transdermal systemic drug delivery, should be evaluated for dermal toxicity. Topical safety studies can be most useful if they are conducted with the final to-be-marketed formulation. The recommended clinical studies are as follows:

- **Cumulative irritancy studies.** These studies should have at least 30 evaluable subjects. If sufficient irritation is noted for the drug under study in phase 2 or phase 3 clinical studies and labeling will include warning regarding the irritation observed, then the cumulative irritancy study can be waived.

- **Allergenicity (contact allergy) studies.** These studies should have at least 200 evaluable subjects if they are to rule out an incidence of greater than a 1.5 percent reaction rate.

- **Phototoxicity and photoallergenicity (photo contact allergy) studies.** These studies can be waived if there is no drug absorbance in the 280 to 700 nM spectrum. The phototoxicity and photoallergenicity studies also can be waived if the patch\textsuperscript{26} under study

\textsuperscript{23} See section 505-1(a) of the FD&C Act.

\textsuperscript{24} See section 505-1(a)(1) and (a)(2)(A) of the FD&C Act.

\textsuperscript{25} When final, this guidance will represent the FDA’s current thinking on this topic.

\textsuperscript{26} The dosage form terminology for products that deliver a drug transdermally is currently under discussion between the FDA and the United States Pharmacopeia.
is opaque or the only indications for use are in areas where there is a minimal chance for
exposure to ultraviolet light.

3. Fixed-Combination Drug Products

New fixed-combination drug products composed of two analgesics, such as an NSAID and an
opiate, are expected to be supported in accordance with the FDA’s combination policy
regulations (21 CFR 300.50). This expectation applies to any fixed-combination drug that has
not been previously approved by the FDA (i.e., where the particular active moieties combined
represent a new combination, even if the components have been previously approved separately).

To satisfy 21 CFR 300.50(a), the application for a new combination of two or more analgesic
drug substances must provide data that demonstrate that “each component makes a contribution
to the claimed effects and the dosage of each component (amount, frequency, duration) is such
that the combination is safe and effective for a significant patient population requiring such
c concurrent therapy as defined in the labeling for the drug.”

Whereas single-dose studies can demonstrate that the fixed-combination drug product is superior
to the single-ingredient analgesics given alone, this would not ordinarily be a sufficient basis for
approval of the fixed-combination drug product. Even for acute pain indications, it is unlikely
that only single doses of such a fixed-combination drug product would be used. Therefore,
studies that compare the fixed-combination drug product to individual component treatment arms
(+/- placebo) over multiple doses would be expected for such drugs. These multiple-dose studies
would allow for elucidation of the contribution of each component to the claimed effect(s) over
time, would often provide valuable information as to the appropriate patient population (as
referred to in 21 CFR 300.50), and would provide additional safety data to inform the risk-
benefit analysis of any such new combination. Support also should be provided for the choice of
the doses of each individual component in a fixed-combination drug product. Most of the points
made in the previous sections of this guidance apply to new fixed-combination drug products,
but sponsors wishing to develop such drugs are encouraged to meet with the relevant review
division before beginning clinical development to discuss the appropriate clinical program.

4. CMC Considerations

Analgesics encompass a variety of dosage forms including solid and liquid oral dosage forms,
transdermal and iontophoretic patches, parenterals, and liquid and semisolid topical
formulations. General guidance pertaining to the CMC of drug development can be found on the
FDA Drugs guidance Web page.27

The usual criteria for developing a dissolution method are applicable and a robust dissolution
method is a necessary tool for assessing in vitro drug release profiles and abuse deterrent
properties.28


28 See the draft guidance for industry Assessment of Abuse Potential of Drugs. When final, this guidance will
represent the FDA’s current thinking on this topic.
5. Specific Labeling Considerations

a. DESCRIPTION section for transdermal products

For transdermal products, the DESCRIPTION section should include the total drug content of the transdermal system along with the release rate (in mg per day).

b. Class labeling

Several categories of analgesic drugs have class labeling in one or more sections. For example:

- **NSAID product** labeling includes a boxed warning for risks of cardiovascular thromboembolic events and gastrointestinal safety. There is also standard language in other sections of the labeling (e.g., WARNINGS AND PRECAUTIONS) and a class Medication Guide.

- **ER/LA opioid analgesic product** labeling has a class-wide boxed warning describing risks associated with Schedule II controlled substances including addiction, abuse, and misuse that can lead to overdose and death, the risk for life-threatening or fatal respiratory depression, the risk for fatal overdose following accidental exposure, and the risk for neonatal opioid withdrawal syndrome in infants born to mothers requiring opioid therapy while pregnant. There also is standard language for the INDICATIONS AND USAGE section and for many subsections under WARNINGS AND PRECAUTIONS.

- **Transmucosal oral fentanyl drugs**, as high potency opioids, have consistent language in much of the product labeling and Medication Guide.

- **Transdermal fentanyl patches** have class labeling for the boxed warning because of their unique pharmacokinetic characteristics, as well as a standardized Medication Guide.