
Guidance for Industry

Analgesic Indications: Developing Drug and Biological Products

DRAFT GUIDANCE

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

**February 2014
Clinical/Medical**

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

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Guidance for Industry¹

Analgesic Indications: Developing Drug and Biological Products

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 This draft guidance is intended to serve as a focus for continued discussions on relevant issues among the Division of Anesthesia, Analgesia, and Addiction Products,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.

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36 not discuss general issues related to statistical analysis or clinical trial design. Those topics are
37 addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10*
38 *Choice of Control Group and Related Issues in Clinical Trials*, respectively.⁵
39

40 FDA's guidance documents, including this guidance, do not establish legally enforceable
41 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
42 be viewed only as recommendations, unless specific regulatory or statutory requirements are
43 cited. The use of the word *should* in Agency guidances means that something is suggested or
44 recommended, but not required.
45

46

II. BACKGROUND

47

48
49 Pain can be categorized according to its duration, acute or chronic, as well as based on other
50 characteristics, such as breakthrough pain, acute episodes of pain that occur on a background of
51 well-controlled, chronic pain. Pain is subjective in nature and is measured by patient self-
52 reporting of its intensity, and other subjective qualities.
53

54 For the purpose of this guidance, *acute pain* is defined as pain that is self-limited and generally
55 requires treatment for no more than up to a few weeks (e.g., postoperative or acute
56 musculoskeletal pain). Even in the setting of acute pain, analgesics generally are used repeatedly
57 over some period of time and not as single-dose treatments. Therefore, although it is important
58 to understand the single-dose analgesic effects of a drug, unless a drug is intended solely for
59 single-dose use, single-dose studies are not considered sufficient to establish the efficacy and
60 safety for drugs indicated for treating acute pain.
61

62 *Chronic pain* is defined as either pain persisting for longer than 1 month beyond resolution of the
63 underlying insult, or pain persisting beyond 3 months. In the context of this guidance, chronic
64 pain refers not only to chronic pain in the terminally ill, but also to chronic pain of various
65 etiologies in persons who are otherwise healthy (e.g., post-traumatic pain, osteoarthritis) or in
66 persons with underlying diseases or conditions that have pain as a prominent manifestation (e.g.,
67 chronic low back pain, spinal cord injury, or diabetic peripheral neuropathy), which is
68 anticipated to persist for 3 months or longer.
69

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

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>.

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76 pain initiated or caused by a primary lesion or dysfunction in the nervous system.⁶ There are a
77 number of neuropathic pain syndromes, based on pathogenesis, affected pathways, and
78 physiological course. In general, neuropathic pain syndromes can be classified as either
79 *peripheral* (when the lesion or dysfunction affects the peripheral nervous system) or *central*
80 (when the lesion or dysfunction affects the central nervous system). Peripheral neuropathic pain
81 syndromes include but are not limited to painful diabetic peripheral neuropathy, postherpetic
82 neuralgia, complex regional pain syndrome, and HIV-associated neuropathy. Central
83 neuropathic pain conditions include but are not limited to postspinal injury pain and poststroke
84 pain.

85
86 *Breakthrough pain* is defined as a transient flare of pain occurring in opioid-tolerant patients
87 experiencing persistent pain otherwise controlled with around-the-clock maintenance opioid
88 therapy consisting of an equivalent of at least 60 milligrams (mg) of morphine per day or an
89 equianalgesic dose of another opioid for 1 week or longer.

90
91 The terms *mild*, *moderate*, or *severe* are often used in a clinical setting to describe pain severity.
92 Although subjective, these terms are commonly used and understood both by health care
93 providers and patients. The terms generally correlate with pain scores on average within the
94 clinical context under evaluation. However, it is understood that when patients report severe
95 pain following a dental extraction, this measurement may not be qualitatively the same as when
96 patients report severe pain following abdominal surgery.

97

98

III. ESTABLISHING INDICATIONS AND CLAIMS FOR ANALGESICS

100

101 We encourage sponsors to state the indications being sought for their analgesics before phase 3
102 studies are initiated, and to discuss these indications with the FDA as early as feasible.⁷

103 Suggested approaches for establishing analgesic indications are provided in the following text,
104 which is divided into sections that discuss procedures for: (1) new molecular entities (NMEs);
105 (2) reformulations of approved drugs; (3) add-on or adjunctive indications; and (4) additional
106 claims.

107

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

114

⁶ As defined by the International Association for the Study of Pain (<http://www.iasp-pain.org/Content/NavigationMenu/GeneralResourceLinks/PainDefinitions/default.htm#Neuropathicpain>).

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>.

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115 A. **NMEs**

116

117 1. *Introduction*

118

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

130

131 2. *Specific/Narrow Pain Indications*

132

133 a. Condition- or population-specific

134

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

142

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

152

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

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

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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.

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- 205 – *Central Neuropathic Pain.* For a stand-alone indication of *the treatment of central*
206 *neuropathic pain*, generally sponsors should conduct at least two trials, each trial in a
207 different central neuropathic condition such as the pain of spinal cord injury,
208 poststroke neuropathic pain, or the pain of multiple sclerosis.
209
- 210 – *General Neuropathic Pain.* For an overall indication of *the treatment of neuropathic*
211 *pain* (both central and peripheral), the recommendations for peripheral neuropathic
212 pain should be fulfilled (i.e., successful trials in each of at least three separate
213 peripheral neuropathic conditions), as well as one successful trial in one central
214 neuropathic condition for a total of at least four trials in four distinct conditions.
215
- 216 • **Chronic Musculoskeletal Pain.** If seeking an indication for the treatment of
217 osteoarthritis, chronic low back pain, or other specific musculoskeletal conditions,
218 sponsors should conduct two successful trials in any one condition for an indication for
219 that condition. However, for the more general indication of *the treatment of chronic*
220 *musculoskeletal pain*, sponsors should conduct two successful trials in one condition plus
221 a successful trial in another musculoskeletal condition (for a total of at least three trials in
222 at least two conditions).
223
 - 224 • **Chronic Pain.** To obtain approval for the broad indication of *the treatment of chronic*
225 *pain*, sponsors should meet the recommendations for general neuropathic pain (i.e., at
226 least four trials per four conditions including one in central neuropathic pain) as outlined
227 above. In addition, sponsors should conduct two successful trials in one non-neuropathic
228 pain condition plus one successful trial in each of two additional non-neuropathic pain
229 conditions (at least four trials per three non-neuropathic conditions). Non-neuropathic
230 pain conditions that are suitable for this purpose include osteoarthritis, chronic low back
231 pain, chronic visceral pain, cancer pain, and fibromyalgia. Thus for an overall indication
232 of the treatment of chronic pain, sponsors should conduct at least eight trials in seven
233 conditions. However, we encourage sponsors to study as many conditions as possible to
234 more fully characterize the properties and potential populations likely to benefit from
235 treatment.
236

237 We encourage sponsors with analgesic drugs for which they are seeking general pain indications
238 (e.g., treatment of the pain of peripheral neuropathy, treatment of the pain of neuropathy, or
239 treatment of musculoskeletal pain) to discuss those development programs with the review
240 division early in development. This is particularly important for sponsors whose drugs fall
241 within well-recognized analgesic drug classes such as opioids, nonsteroidal anti-inflammatory
242 drugs (NSAIDs), or local anesthetics, because additional flexibility and individualization of the
243 development programs may be possible.
244

B. Reformulations of Approved Drugs

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

C. Add-On or Adjunctive Indications

261
262 There may be situations in which drugs are studied as add-ons or adjunctive therapy in subjects
263 receiving concomitant treatment with an existing standard of care. This situation may be
264 appropriate for drugs expected to have an effect only in conjunction with concomitant treatment
265 or in patient populations that cannot be studied without the underlying therapy. In cases where
266 the efficacy data come from such adjunctive use, the drug would likely receive an indication as
267 an adjunctive therapy in the setting under which it was studied).

D. Additional Claims

270
271 Additional claims of treatment benefit based on clinical domains relevant to analgesia may be
272 appropriate for some clinical populations that are defined by those domains. Claims of treatment
273 benefit should represent findings that are not directly a result of a change in pain, but if subjects
274 sleep better merely because they have less pain, the improved sleep is not a direct positive effect
275 of the drug. For example, fibromyalgia is a syndrome that includes pain as well as fatigue and
276 trouble sleeping. A properly designed evaluation of sleep during a clinical trial in subjects with
277 fibromyalgia may demonstrate positive effects for pain as well as sleep. In contrast, subjects
278 treated with a sedating analgesic may sleep more, but this may not represent improved sleep, and
279 these subjects may experience the sedating effects during the day as well. Replicated findings
280 from adequately designed studies incorporating instruments demonstrating substantial, clinically
281 meaningful improvement can support such claims.

282
283 Early in drug development, sponsors seeking treatment benefit claims in addition to analgesia
284 (e.g., improved physical or emotional functioning) should determine whether a well-defined and
285 reliable patient-reported outcome (PRO) measure exists to assess and measure the concept of
286 interest and context of use or whether a new measure should be developed. The guidance for
287 industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support*
288 *Labeling Claims* delineates the evidentiary standards by which the FDA reviews a measure for
289 its adequacy to support labeling claims. If additional treatment benefit claims are sought, it is
290 important to also assess the drug's effect on pain (i.e., its analgesic effect) in the same studies,
291 because it is not possible to interpret the effect of treatment on distal concepts (e.g., less
292 constipation) without also evaluating the core symptom under investigation (i.e., pain). We

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.

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293 recommend that sponsors prespecify the analysis of endpoints to support additional claims,
294 including methods to address multiplicity.

295

296

IV. DEVELOPMENT PROGRAM

297

298
299 Analgesic development involves important concepts that sponsors should consider during drug
300 development, such as the duration of drug exposure for the treatment of acute and chronic pain
301 and the subjective nature of pain intensity measurement. It is important that the spectrum of
302 clinical studies planned during analgesic development provide an adequate characterization of
303 the clinical, pharmacological, and, when feasible, pharmacodynamic behavior of the drug.

304

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

313

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

323

A. General Considerations

324

325

1. Early Phase Clinical Development

326

327

328 Generally, early analgesic development should be consistent with the standard phase 1 and phase
329 2 development objectives. Pharmacokinetic characteristics and tolerability should be explored in
330 appropriate volunteers or stable, relatively healthy patient populations. One special
331 consideration to keep in mind when planning early trials of analgesics when dosing is less certain
332 is that pain is a highly activating stimulus. Doses of central nervous system (CNS) active drugs
333 that are tolerated in subjects with pain may be overly sedating or may depress respiratory drive in
334 healthy volunteers. Although subjects in some early studies of opioids can be protected from
335 oversedation and respiratory depression with the use of opioid antagonists, there are no reversal
336 or blocking agents currently available for other existing analgesic drugs or NMEs under
337 development. Sponsors should monitor subjects for early signs of CNS or respiratory depression

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338 and appropriate interventions should be planned and specified in advance of initiating clinical
339 trials.

340
341 We strongly recommend that sponsors include in the protocol detailed information for managing
342 adverse events along with documentation of the immediate availability of staff capable of
343 managing emergencies (e.g., trained in airway management). In general, reliance on transport to
344 an emergency room as the primary support for emergency events may not be appropriate.
345 Stopping criteria for ending further dosing of a dose level, or for discontinuing an individual
346 from the study, should be included in all study protocols. Criteria should be based on the
347 toxicity findings from nonclinical studies, as well as basic vital signs, physical exam, or
348 laboratory parameters as appropriate to the situation. As always, but especially in the absence of
349 any potential benefit for healthy volunteers, risks should be clearly and carefully delineated in
350 the informed consent document. See 21 CFR parts 50 and 56.

351
352 For the earliest clinical studies during first-in-human exposure for any NME or reformulations of
353 existing drugs that offer substantially greater risk than the original formulation, careful
354 consideration should be given to dosing subjects within any dose cohort one at a time rather than
355 simultaneously. The time between subjects should be based on the anticipated half-life of the
356 drug. This is important for two reasons. For unexpected adverse events, initially dosing one
357 subject at a time permits an opportunity to reevaluate the appropriateness of further testing of
358 that dose and of the drug. For adverse events that require intervention, dosing subjects one at a
359 time permits the staff to more closely monitor each individual subject.

360
361 Although there is no particular minimum number of studies to be conducted during phase 1 and
362 phase 2, we strongly encourage sponsors to explore a broad range of doses to begin the
363 evaluation for a dose response as well as to provide early information about the safety profile of
364 the drug. Dropouts caused by adverse events can have a substantial negative effect on data
365 collection and consequently on interpretation and adequacy of phase 3 efficacy results. During
366 phase 2, it is important to explore ways to minimize adverse event occurrence, particularly
367 adverse events that may occur during dose titration. Any information that leads to study designs
368 that can minimize dropouts during the observation period (e.g., lengthening the titration period to
369 minimize adverse event occurrence) may greatly improve the likelihood of success of phase 3
370 studies.

371
372 If possible, identification of a ceiling effect for efficacy during phase 2 can be informative for
373 future study design considerations and for drug labeling. We encourage sponsors to explore
374 exposure-response relationships for efficacy over a range of doses to help select the dose or
375 doses for use in phase 3 trials.

376
377 Single-dose studies may provide useful information about several characteristics of the drug
378 during phase 1 and phase 2, but are not considered adequate to support a finding of efficacy for a
379 drug intended for multiple-dose use.

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381 2. *Drug Development Population*

382
383 The intended target population for an analgesic indication depends on whether the drug is
384 intended for use in acute or chronic pain, the severity of pain suitable for management with the
385 drug, and the overall risk-benefit balance of the drug. For example, a drug intended for
386 intrathecal use may be indicated for a patient population with pain that is severe and intractable
387 and suitable for the inherent risks of an implantable pump. In contrast, a topical analgesic
388 associated with minimal risk and indicated for the management of local pain may be indicated
389 for a broader population.

390 391 3. *Efficacy Endpoint Considerations*

392
393 Because pain is a subjective experience, the choice of an adequate instrument to measure the
394 primary endpoint is critical to demonstrating the efficacy of an analgesic. Therefore, it is
395 important to consider whether a well-defined and reliable instrument exists or can be developed.
396 It is also important that measures be based on scales or instruments that have been adequately
397 developed for use in the population to be studied, and that the instruments be appropriate for use
398 in the setting of a clinical trial to measure change over time. Novel instruments should have
399 documented development and assessment of measurement properties available before use in
400 phase 3 efficacy trials.¹⁰ The development of novel instruments should be discussed with the
401 FDA early in drug development.¹¹

402
403 Efficacy endpoints in an analgesic trial should reflect a direct rating of pain intensity by the
404 subject for all settings in which subjects can communicate in a reliable manner. We recommend
405 the use of a well-defined and reliable PRO measure of the subject's pain intensity. We
406 discourage an assessment that requires the subject to report on the concept of pain relief because
407 the subject must compare their current state to a previous state, requiring additional mental
408 processing of the overall experience. Additionally, pain relief scales can take into account not
409 just a difference in pain intensity, but also consideration of how efficacy may be affected by
410 adverse effects; therefore, the scales may represent a rating of a different concept for different
411 subjects.

412
413 In case of young children or subjects who cannot provide self-report, observers (e.g., parents,
414 caregivers) can report on observable indicators of disease or health condition through
415 measurement of an observer-reported outcome (ObsRO). ObsRO concepts include only those
416 events, behaviors, or signs that can be detected by an observer's senses (i.e., wincing, crying, or
417 squirming). An observer cannot validly rate a subject's pain intensity and the FDA does not
418 consider an instrument that requires an observer to do so to be well-defined or reliable.
419 Similarly, a clinician-reported outcome instrument to be completed by the study investigator
420 should be limited to those concepts that are observable.

421

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.

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422 Composite scales that are composed of multiple domains generally should be avoided as the
423 primary outcome in an analgesic trial. Multidomain scales may be difficult to interpret across a
424 population, as the same change in overall score can be based on differing patterns of response to
425 the individual domain scores. Multi-item scales within a given domain may be useful. In
426 contrast, the definition of a *responder* can include multiple components such as pain intensity,
427 use of rescue, and ability to complete the study period and may be an acceptable primary
428 outcome metric.

429
430 Pain intensity should be evaluated over an appropriate multiple-dose period suitable to support
431 the indication sought. The endpoint instrument's recall period for assessing pain should be
432 appropriate for the type of pain studied and the planned study design. Generally, we recommend
433 use of an instrument that asks the subject to assess his or her worst pain over a relatively short
434 time period, and no longer than the past 24 hours, with the assessment occurring at the same time
435 each day.

436
437 When pain intensity is the primary efficacy endpoint, it is important to take into consideration
438 the use of rescue medication as a secondary outcome measure. (See additional discussion on this
439 topic below.)

440

441 4. *Safety Considerations*

442

443 a. Clinical trial elements

444

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

447

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

457

458 • **Stopping criteria.** The grading of toxicity in a clinical trial for the purposes of stopping
459 criteria or creating the final report should be appropriate to the situation. For instance,
460 the National Cancer Institute Common Terminology Criteria for Adverse Events
461 (CTCAE)¹² were created for use in oncology clinical trials and generally are not
462 appropriate criteria for grading toxicity in an analgesic trial, particularly early trials in
463 healthy volunteers. The categories are broad and toxicities found to be higher than Grade
464 1, for most body systems, would be unacceptable during clinical trials for analgesics.

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).

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465 Therefore, the sponsor should incorporate stopping criteria that are suitable for the
466 circumstances of the clinical trial.

467

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

475

476 b. Safety database

477

478 The size of the safety database needed to support approval for an acute or chronic pain indication
479 depends on a number of factors, including whether the drug is an NME or a reformulation of a
480 known drug substance, the nature of the safety findings from the clinical trials, and the
481 nonclinical data for the drug under development. For the safety evaluation of an NME intended
482 for treatment of chronic pain, we recommend sponsors refer to the ICH guidance for industry
483 *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-*
484 *Term Treatment of Non-Life-Threatening Conditions* for drugs intended for long-term treatment
485 of non-life-threatening conditions and to the guidance for industry *Premarketing Risk*
486 *Assessment*. These guidances make recommendations on the minimum size of the database.
487 These minimums also should apply to a proposed new chronic indication for a drug previously
488 approved for an acute indication only. A safety database larger than recommended in these
489 guidances may be warranted for a number of reasons (many of which are discussed in these
490 guidances), including safety signals emerging as more clinical data become available.

491

492 For reformulations of drugs with existing chronic pain indications, the size of the safety database
493 should reflect the differences from existing formulations of the drug and the gap in safety data
494 expected from these differences. For example, an oral drug indicated for chronic pain might be
495 reformulated into a transdermal formulation. In general, in the case of reformulated drugs, the
496 amount of safety data that should be collected to support safe use depends on differences in
497 pharmacokinetics, particularly if the new formulation resulted in a drug with a delayed C_{max} and
498 a prolonged half-life. To determine an appropriate number of subjects for the safety database for
499 a drug previously approved for a nonanalgesic indication, sponsors should consider the extent of
500 differences between the previous patient population studied and the analgesic population under
501 evaluation, and whether the differences alter the risk for adverse reactions.

502

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

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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.¹³ 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.¹⁴ 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.¹⁵

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

¹³ See 21 U.S.C. 801 et seq.; 21 CFR 314.50(d)(5)(vii).

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.

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552
553 The fifth PMR is a clinical trial to estimate the serious risk of the development of hyperalgesia
554 following use of ER/LA opioid analgesics for at least 1 year to treat chronic pain with a
555 suggested assessment of the development of tolerance following use of ER/LA opioid analgesics.
556

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

563
564 Sponsors of all new NSAIDs should discuss with the review division as early as possible the
565 need for trials to assess cardiovascular risk for thromboembolic events including myocardial
566 infarction, sudden cardiac death, and cerebrovascular accident. Safety monitoring for this trial
567 type should include a data monitoring committee with prespecified plans for adjudication of all
568 pertinent events. It is also important to record adequate information to understand the potential
569 effects of the drug on blood pressure, the occurrence of congestive heart failure, peripheral
570 edema, renal function, gastrointestinal toxicity (e.g., perforations, obstructions, bleeds), and liver
571 function during all clinical trials for these drugs.

572 573 d. New routes of administration

574
575 New routes of administration may raise potential route-related safety concerns. Information
576 should be collected as appropriate for the route of administration. Topical products can be
577 intended for local drug delivery or can be intended to provide transdermal systemic drug
578 delivery. For these products it is important to include an assessment of dermal toxicity. This
579 should include cumulative irritancy studies, allergenicity (contact allergy) studies, and
580 phototoxicity and photoallergenicity (photo contact allergy) studies (see section IV.C.2., Skin
581 Studies for Topical Products). It is also important to examine the effects of heat on the delivery
582 of drug from topical products, both external heat and the effects of exercise. For products
583 intended to deliver the drug to local tissue, with anticipated limited systemic toxicity, it is also
584 important to study a maximal exposure situation. As one example, for a topical NSAID cream
585 intended to treat arthritis pain, maximal exposure can be evaluated after application to two knees
586 and two hands. In addition, residual drug in patch formulations may place household contacts at
587 risk for accidental exposure. Specific methods for safe disposal should be developed to
588 minimize this risk.

589
590 Studies of drugs administered by the intranasal route of administration should include data from
591 visual inspections of mucous membranes. Studies of drugs by inhalational route of
592 administration should include thorough pulmonary safety assessments, including, at a minimum,
593 pulmonary function testing. Spray pattern and droplet size should be characterized for all
594 inhalational and intranasal drugs early in development.
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596 New routes of administration for approved drugs (e.g., pulmonary administration of a drug
597 approved previously for oral use) should include appropriate nonclinical bridging studies
598 focusing on the toxicities specific to the new route.

599

B. Specific Efficacy Trial Considerations

600

1. Trial Design

601

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

614

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

624

a. Use of rescue medication

625

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

631

b. Add-on design

632

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

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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

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688 endpoint, sponsors are encouraged to measure both time to onset of detectable pain relief and to
689 meaningful pain relief. Repeated measures of pain intensity and pain relief over the trial period
690 should establish the time of maximal effect of the drug. The duration of analgesia generally is
691 defined by the median time to a request for rescue or re-medication. It is important that onset of
692 analgesia, duration of effect, and magnitude of effect be determined in clinically relevant patient
693 populations.

694 3. *Multiple-Dose Data*

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

700 a. Acute pain

701
702 In many acute pain settings, pain intensity changes over a relatively short period of time, which
703 can present challenges in designing a trial. Nevertheless, it is important to explore the
704 appropriate use of a drug during a multiple-dose period. For parenteral drugs for use in the
705 postoperative period, the primary efficacy period should be no less than 24 hours for one trial
706 and 48 hours for the second trial when a second trial is needed, but longer periods of time also
707 may be appropriate and are encouraged when feasible. However, we strongly encourage the trial
708 duration to extend for as long as it is suitable for subjects to remain on the parenteral therapy to
709 obtain additional efficacy and safety information.

710
711 For oral analgesics, longer efficacy studies are encouraged. We recommend confirming an
712 appropriate dosing interval during multiple-dose treatment, taking into consideration
713 pharmacokinetic characteristics and the duration of effect determined during earlier trials.
714 Important considerations to include in designing these trials are the magnitude of effect and the
715 effects of rescue medication use on re-dosing and efficacy outcome measures. To avoid
716 interference in efficacy measures at scheduled times because of the use of rescue medication,
717 sponsors can make pain assessments before rescue, asking subjects to report the pain intensity at
718 the current time with no recall period, and imputed to the following scheduled assessment time.
719 The primary efficacy endpoint can be based on a time-weighted analysis over the trial period.

720
721 Analgesics considered appropriate for the management of acute pain are often used on a chronic,
722 intermittent basis. To understand the durability of efficacy in this setting, and perhaps more
723 importantly, the safety of this type of use, we recommend studying such drugs under these
724 conditions of use. An important question to consider is whether efficacy is sustained with
725 chronic, intermittent use, particularly when around-the-clock dosing is no longer necessary. One
726 approach to this evaluation is to permit subjects to use the analgesic on an as-needed basis
727 following a multiple-dose, around-the-clock trial period. An additional efficacy analysis can
728 then be performed to determine whether the drug continues to provide a reduction in pain.

730 b. Chronic pain

731
732 Consistent with studies of many drugs intended for chronic administration for other indications,
733 we recommend at least a 3-month duration for studies evaluating analgesia in chronic pain. A

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734 shorter trial duration can be considered in situations that are not suitable for a full 3-month trial
735 because of clinical constraints (e.g., terminal cancer pain). It is important that the efficacy
736 outcome include pain assessments throughout the trial and also at the end of the trial. The recall
737 period should be specified as well as the pain concept sought. For example, the subjects can be
738 asked to rate the worst pain over a 24-hour recall period. Such assessments ensure that
739 analgesics in this chronic use setting can be evaluated for the presence of consistent and durable
740 efficacy. The primary efficacy endpoint should be evaluated as a change in pain intensity from
741 baseline to the end of the double-blind period of the trial. An analysis of the pain intensity as a
742 time-weighted analysis can be highly informative and is recommended as a secondary endpoint.

743
744 Demonstrating efficacy in a 12-week trial of chronic pain with an opioid analgesic can be
745 challenging. Relatively high rates of early discontinuations, often caused by adverse events, can
746 lead to great difficulty in evaluating missing data. All imputation methods offer strengths and
747 weaknesses that can affect the results. Opioids typically are titrated to an effective dose in
748 clinical practice and have no ceiling effect for analgesia. Therefore, an upper limit for the dosing
749 range need not be identified. As previously discussed, clinical trials of opioids, particularly
750 opioid reformulations, may be particularly well suited for a titrate-to-effect design. In this trial
751 type, subjects are titrated to an effective and tolerable dose. This can be done as an open-label
752 titration followed by randomization to active or placebo treatment groups for subjects who meet
753 criteria for successful titration. Another option is to randomize subjects and then titrate to an
754 effective and tolerable dose.

755
756 Analgesics that belong to a drug class with a well-defined ceiling effect for efficacy and a dosing
757 range that encompasses only a limited number of doses may be better suited for clinical trials
758 with a parallel, fixed-dose design. This design type provides an opportunity to establish a dose
759 response across doses and, for new drugs, identify the top of the dosing range. NSAIDs are an
760 example of a drug class that has been studied successfully with this design. In contrast to
761 opioids, NSAIDs generally result in fewer bothersome adverse events such as nausea and
762 sedation after dosing has been initiated, so high dropout rates are less common in 12-week trials.
763 However, for approved analgesics with an identified dosing range and a known dose-response
764 relationship for side effect tolerability, when a new analgesic indication is sought, a titrate-to-
765 effect design may be acceptable. This depends on the similarities of the new patient population
766 as compared to the patient population associated with the existing indication. If the populations
767 differ substantially in age, comorbidities, or concomitant medications, a safe and effective dosing
768 range may need to be established for the new indication. Parallel-arm, fixed-dose trials should
769 be considered for the purpose of establishing evidence of a dose response to support the
770 proposed doses.

771
772 NMEs should be adequately explored in phase 2 to determine the best approach to trial design in
773 phase 3. An end-of-phase 2 meeting is strongly advised so that the division can provide input on
774 that approach.

775 776 4. *Trial Population*

777
778 We encourage sponsors to apply the following principles to subject selection in analgesic clinical
779 trials. Patient populations in phase 3 clinical trials should represent as much as possible those

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780 patients reasonably expected to use the drug after it is marketed. This is particularly important
781 for drugs that may have general pain claims. As a general rule, the characteristics of the
782 population should not be unnecessarily restrictive. In some clinical development programs, it
783 may be useful for one phase 3 clinical trial to have entry criteria that are more narrowly defined,
784 allowing for enrichment where appropriate, while a second clinical trial for the same indication
785 may have broader entry criteria, the results of which can help address generalizability.

786
787 Although efficacy should be replicated in typical drug development programs, we strongly
788 encourage sponsors to avoid conducting two identical trials of the same population as the sole
789 support for efficacy, particularly with NMEs. It is critical that a variety of clinical situations
790 where the drug may be effective and useful be adequately explored. This is particularly
791 important for NMEs. We encourage sponsors to evaluate a broad range of pain populations for
792 NMEs that are the first in a new class of analgesics. Trial populations should include subjects
793 with nociceptive somatic and visceral pain and neuropathic pain conditions to enable
794 demonstration of the most appropriate populations for inclusion in the drug's indication.

795
796 In situations when pain is a manifestation of systemic disease, it may be important to quantify in
797 the protocol the extent and severity of the underlying systemic disease at the start of the clinical
798 trial. It is also important to ensure that all clinical trial subjects have access to appropriate care
799 for the underlying disease throughout the course of the clinical trial. When feasible, attempts
800 should be made to keep treatment of the underlying disease stable during clinical trials. When
801 changes to the subject's medical treatment outside of the trial become necessary, it is important
802 to record the reasons underlying those changes on the case report form.

803
804 For all analgesic efficacy trials, the size of the enrollment should be based on the number of
805 subjects needed to demonstrate a meaningful difference in treatment arms and should not be so
806 large as to give statistical significance to a difference in effect size that is too small to have
807 clinical relevance. This consideration should be addressed in the powering discussion of the
808 statistical plan.

809 810 5. *Entry Criteria*

811
812 The inclusion and exclusion criteria should describe characteristics of the trial population that
813 support its ability to provide appropriate data for the proposed indication.

814
815 Some criteria are important to assess when designing analgesic efficacy trials. One criterion is
816 whether individuals with a prior history of substance abuse can be included in the trial. If this is
817 to be permitted, specific monitoring of substance abuse or misuse should be incorporated into the
818 trial. Another criterion is whether individuals are involved in activities that can provide
819 secondary gain that may interfere with assessments. Defining a population as refractory to other
820 analgesic treatments or as opioid tolerant are other criteria that may be important to consider.

821
822 We recommend sponsors give consideration to the role of ongoing concomitant medications for
823 the management of pain in analgesic clinical trials. The following general principles should be
824 considered:

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- 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

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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.

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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

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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

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872 development because applicants submitting NDAs (or supplements) for a new active ingredient,
873 new indication, new dosage form, new dosing regimen, or new route of administration of a
874 drug¹⁶ are required to submit pediatric study plans no later than 60 days after an end-of-phase 2
875 meeting, unless another time has been separately agreed upon.¹⁷ For further information about
876 required pediatric studies, we recommend sponsors refer to the Pediatric Research Equity Act¹⁸
877 as amended by the Food and Drug Administration Safety and Innovation Act.¹⁹
878

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

880
881 For NMEs of either a new drug class or a class of drugs that is still establishing its safety and
882 efficacy profile for analgesia in adults (such as the serotonin/norepinephrine reuptake inhibitor
883 class), full efficacy, safety, and pharmacokinetic studies should be conducted in the full age
884 range of pediatric subjects.
885

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

887
888 When establishing a pediatric pain indication for these drug types, extrapolation of adult efficacy
889 data down to the age of 2 years may be appropriate provided: (1) the drug's mechanism of
890 action is known; (2) this mechanism is similar in the pediatric and adult populations; (3) the
891 metabolic pathway is established and is similar between adult and pediatric populations; and (4)
892 the condition(s) being treated are considered similar in adults and children. Drug classes that fit
893 into this category and thus generally would allow for the extrapolation of adult efficacy data
894 down to the age of 2 years include the opioids, nonsteroidal anti-inflammatory agents, local
895 anesthetics, and acetaminophen. Pharmacokinetic studies and safety data should be obtained to
896 conclusively permit the extrapolation of adult data to this population.
897

898 For pediatric subjects under the age of 2 years, full efficacy, safety, and pharmacokinetic studies
899 should be conducted. However, we would be willing to consider alternative study designs such
900 as add-on studies where an endpoint could be a reduction in amount of rescue medication needed
901 or a decrease in the need for caregiver- or nurse-controlled analgesia so long as the study design
902 would allow for the determination that the drug was exerting an analgesic effect using a well-
903 defined and reliable observation-based measure of signs thought to be related to pain in the target
904 patient population and context of use (e.g., crying, arching back).
905

906 8. *Dose Selection*

907
908 Dose selection for analgesic trials should take into consideration the nature of the drug and likely
909 concomitant medications. For CNS depressants, concomitant use of other CNS depressants
910 should be minimized in early trials and explored cautiously later, if such use is expected in the
911 clinical setting. Protocols should include an adequate titration period with monitoring for CNS

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

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

¹⁸ See Public Law 108-155 (2003).

¹⁹ See Public Law 112-144 (2012).

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912 depression. NMEs should be evaluated for possible withdrawal syndromes, and whether known
913 or expected, adequate tapering periods should be incorporated at the end of the trial. In NSAID
914 trials, sponsors should consider dosing with respect to renal function.

915

916 9. *Choice of Comparators*

917

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

925

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

933

934 10. *Efficacy Endpoints*

935

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

943

944 a. *Pain intensity*

945

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

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955 b. Function

956
957 Patients often experience some negative effects of pain on aspects of physical function or
958 emotional function, particularly with chronic pain. In addition, drug-related adverse events can
959 affect function. It is important to collect information on the effects of treatment on function,
960 particularly for chronic pain indications, to fully inform the risk-benefit assessment. We
961 encourage the use of existing well-defined and reliable scales specifically developed and tested
962 in the patient population under evaluation, sensitive enough to detect a deficit, and responsive
963 enough to detect a clinically meaningful change over time. We also encourage efforts to develop
964 new well-defined and reliable instruments where necessary.^{20,21}

966 c. Health-related quality of life

967
968 Health-related quality of life (HRQL) is a multidomain concept that represents the subject's
969 overall perception of the effect of an illness and its treatment. An HRQL measure captures, at a
970 minimum, physical, psychological (including emotional and cognitive), and social functioning.
971 In general, HRQL instruments are not appropriate as primary endpoints for several reasons: (1)
972 some HRQL instruments include inappropriate items for drug development trials (e.g., financial
973 well-being); (2) concepts and domains measured are distal to the effect of treatment; (3) the
974 proximal effects of treatment on how subjects feel and function may not be captured (e.g., items
975 reflecting personal well-being may be too far *downstream* to reflect treatment benefit); and (4)
976 they reflect or respond to other causal factors that increase variability of the measurement and
977 impair the interpretation of treatment effect.

978
979 The inclusion of distal attributes of well-being that typify HRQL questionnaires attenuate the
980 overall ability of the measure to detect change. This occurs even when improvements in
981 personal well-being items more securely reflect treatment benefits. Even expected
982 improvements in personal relationships or social participation can be less likely to show change
983 across the duration of the clinical trial. A claim based on HRQL measurement to demonstrate
984 investigational treatment benefit can be misleading if treatment adverse effects are not yet fully
985 known and the HRQL instrument does not prospectively measure the effect of relevant adverse
986 effects on HRQL. Overall, HRQL is inappropriate as a primary endpoint, likely challenging as a
987 secondary endpoint, but certainly welcome as an exploratory endpoint when an instrument
988 addresses concepts about which subjects express concern.

990 d. Rescue medication

991
992 In studies where rescue medications are allowed, it is critical to record, quantify, and analyze
993 rescue medication use. The protocol should identify what type and amount of rescue medication
994 will be acceptable during the study. Changes in pain intensity and pain relief measures cannot be
995 meaningfully interpreted in the absence of information on rescue medication use. In the absence
996 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*.

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997 important that protocols specify the drug or drugs permitted as the rescue medication. It is also
998 important that the protocol specify at what level of pain, based on the scales or other assessments
999 used to measure pain intensity, rescue medication can or should be administered, and the timing
1000 of pain measurements in relation to allowed rescue medication use.

1001
1002 e. Global single-item assessment

1003
1004 General single-item assessments cannot be considered well-defined and reliable and are not
1005 recommended for use to support claims of treatment benefit. Global assessments generally are
1006 measured by single questions that use a categorical or visual analog scale for scoring overall
1007 response to treatment or status of the subject. Global assessments aim to elucidate the subject's
1008 integrated, overall experience with the analgesic, rather than an additional assessment of efficacy
1009 or safety. They are sometimes used as exploratory endpoints to use when interpreting change
1010 using other measures. It is impossible to identify one specific question that best captures a
1011 subject's experience in all circumstances and for all purposes. Although useful as a means of
1012 broadly assessing the subject status and helping to integrate the effects of drug efficacy and
1013 safety from the perspective of the subject, the interpretation of the question and resulting
1014 response will differ from one subject to the next. However, global assessments may be useful for
1015 providing context for understanding the efficacy and safety findings.

1016
1017 f. Opioid sparing

1018
1019 Opioid sparing resulting from the use of a nonopioid therapy can be considered an outcome
1020 measure in some chronic pain states or pain processes. It can provide evidence of analgesic
1021 efficacy in a manner similar to the assessment of amount of rescue medication use. However, for
1022 drugs intended only for concomitant use with opioids, a reduction in opioid use alone may not
1023 have clinical significance unless additional benefit can be demonstrated, such as fewer opioid-
1024 related adverse events.

1025
1026 g. Sleep

1027
1028 We encourage attempts to evaluate effects of analgesics on sleep, but such attempts may not be
1029 appropriate to support a specific sleep-related claim unless found to provide a clinically and
1030 statistically additional benefit to the analgesic effect. A single-item general assessment of a
1031 complex multidomain concept such as sleep quality cannot be considered well-defined and
1032 reliable to support a claim. Sleep disorders include difficulty falling asleep, staying asleep, and
1033 waking up refreshed. We encourage using well-defined and reliable methods for measuring the
1034 effects of analgesics on sleep. It is important to also consider the use of indirect assessments of
1035 sleep using clinic-based tests (e.g., polysomnography) if sleep-related claims are being sought.

1036
1037 h. Additional measures

1038
1039 Other well-defined and reliable PRO measures also can be incorporated into analgesic drug trials
1040 and can, if used in an appropriately designed trial, serve as the basis of a labeling claim.
1041 Sponsors are encouraged to discuss plans to use such additional outcomes with the division.
1042

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1043 11. *Statistical Considerations*

1044
1045 The statistical analysis of analgesic trials has two related but distinct goals. First, it should be
1046 demonstrated, at an acceptable level of confidence, that the investigational drug has a beneficial
1047 effect. Second, it is important to describe the drug's efficacy in some detail.

1048
1049 The first goal normally should be addressed by significance testing, which controls the
1050 probability of falsely finding that an ineffective drug is effective. As the probability of such
1051 false findings is multiplied when there are multiple tests, it is important to specify in advance a
1052 single, primary analysis without whose success the trial will not be claimed to provide evidence
1053 of efficacy.

1054
1055 There should be a multidimensional description of the drug's efficacy. Questions to be answered
1056 can include: How large were the effects? How did the effects vary from subject to subject?
1057 How soon after dosing did the effects appear, and how long did efficacy last? The answers to
1058 these questions will certainly involve measurements at multiple time points, and they may
1059 involve different kinds of measurements as well.

1060 1061 a. Demonstrating efficacy

1062
1063 It is important to choose a single, clinically relevant statistical test that is expected to reliably
1064 distinguish the experimental drug from the control. This distinction is likely to be based on a
1065 visual or numerical rating of pain intensity, or a categorical rating with several categories. It
1066 may be a single rating at a given point in time, or an average or other summary of several ratings
1067 over a period of time. For chronic conditions, however, the outcomes at the end of the trial are
1068 of special interest, as they may be the best indicators of benefit in the longer term.

1069
1070 A responder analysis, in which the outcome for each subject is summarized as a success or a
1071 failure based on a single cut-off point (e.g., 30 percent reduction in pain (with early
1072 discontinuation counted as a failure)), can be used. As discussed below, such analyses are easy
1073 for clinicians to interpret, and they can greatly mitigate the problems of missing data. There may
1074 be a substantial loss of information, however, when detailed observations on each subject are
1075 reduced to a single dichotomy. Therefore, this form of a responder analysis may not be the most
1076 powerful method of demonstrating a beneficial effect. However, a responder analysis that
1077 evaluates responder status across the full range of outcomes for an endpoint can be helpful in
1078 describing the effects of the experimental treatment. Sponsors are encouraged to include a
1079 presentation of these analyses in the package insert to better inform prescribers of the trial
1080 outcome. The percent of subjects, y , achieving a reduction in pain of x percent, for x ranging
1081 from 0 to 100, can be plotted against y^* (cumulative distribution function).

1082
1083 The primary test for a numerical or even a categorical score can be based on a mean across
1084 subjects. This is not because the average of different subjects' pain scores is itself a meaningful
1085 quantity, as it may not be. Rather, it provides a valid, sensitive test for systematic differences
1086 between groups in individual scores. For the sample sizes likely to be needed in analgesic trials,
1087 the two-sample t-test is robust against departures from normality and therefore can be considered
1088 essentially nonparametric. Rank-based nonparametric methods also may be appropriate. Again,

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1089 however, it is important to choose the method in advance to avoid the problems associated with
1090 multiplicity. Protocols that specify alternative methods *as needed* are troublesome, because there
1091 may not be agreement on whether or not they are needed. We recommend specifying in the
1092 protocol a single, sufficiently robust method, whether rank-based or nominally parametric.

1093

1094

b. Descriptive statistics

1095

1096 We recommend sponsors provide detailed descriptions of the clinically relevant effects of the
1097 analgesic drug. The time course of effects is particularly important because it will inform health
1098 care providers on the range of dosing intervals that may be useful. It will, therefore, often be
1099 useful to report measures of pain at multiple time points by descriptive statistics (i.e., inferential
1100 statistics beyond those for primary efficacy variables generally are not appropriate for inclusion
1101 in labeling). The need for such a detailed, multifaceted description of effects is not in conflict
1102 with the need for a single, primary analysis to demonstrate that the drug has an effect.

1103

1104 It is important for descriptive analyses to represent the variability from subject to subject. Plots
1105 of cumulative distributions, boxplots, or standard deviations can be useful for this purpose. P-
1106 values, or even confidence intervals or standard errors, are not useful in portraying individual
1107 variability; rather, they are measures of the uncertainty in mean values. We recommend
1108 including descriptive statistics if they are useful and credible, not just if they are statistically
1109 *significant*.

1110

1111

c. Missing data

1112

1113 It is important that every appropriate means be taken to minimize dropouts. However, we
1114 acknowledge that treatment discontinuations are inevitable in analgesic trials.

1115

1116 It is a common finding in some analgesic drug classes that subjects dropping out from the
1117 placebo group and active treatment group differ with respect to reason for early discontinuation.
1118 Early discontinuations because of a lack of efficacy often are more prevalent in the placebo
1119 group, whereas early discontinuations because of adverse events often are more prevalent in the
1120 active treatment group. Thus, even when the treatment groups are balanced at baseline by
1121 randomization, they no longer comprise comparable subjects at the end of the trial. Each group
1122 has remaining whatever subjects did not experience intolerable side effects or lack of efficacy,
1123 and this subset of subjects is systematically different for different treatments. For this reason,
1124 comparison of completers only is not useful as a primary analysis.

1125

1126 In general, it is important that bad outcomes be attributed to subjects who were unable to
1127 complete the course of treatment because such subjects did not benefit from the treatment. This
1128 attribution is often misunderstood as a matter of estimation, but there is in a sense nothing to
1129 estimate. The *missing* outcomes are not merely unobserved, they are nonexistent.

1130

1131 In the past, bad outcomes on analgesic trials were assigned by a single imputation strategy such
1132 as last observation carried forward (LOCF). The use of a LOCF strategy in multiple-dose trials,
1133 however, might result in good pain scores being carried forward for subjects who experienced
1134 relief of pain before dropping out because of excessive toxicity (e.g., a potentially excessive

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1135 dose). The LOCF method in such a case would assign misleading, good outcomes to such
1136 subjects. In contrast, the baseline observation carried forward method would appear to have
1137 some pragmatic justification because a bad outcome would be assigned to all subjects dropping
1138 out. However, the method would not reflect the statistical uncertainty or variability about the
1139 imputation and could consequently lead to inaccurate inferences. This is true of all single-
1140 imputation strategies. Therefore, we do not recommend their use in multiple-dose, chronic pain
1141 trials.

1142
1143 We recommend some other method be used to avoid attributing an overall benefit to a drug that
1144 does not benefit individual subjects. Possible methods may include model-based approaches that
1145 address the specific needs of analgesic trials. The model should be specified and the assumptions
1146 underlying the model should be justified. Another possible strategy may be to use a composite
1147 outcome that incorporates dropout in the definition of a responder (see the responder analysis
1148 described in section IV.B.11.a., Demonstrating efficacy). Regardless of the technique used to
1149 handle missing data, sensitivity analyses should be performed to assess the effects of the analytic
1150 method on the results.

1151
1152 Finally, because the analytic strategy to handle missing data for the primary efficacy evaluation
1153 is critically important, that choice should be prespecified before the blind is broken. Preferably,
1154 the statistical analysis plan should be finalized before trial initiation.

d. Covariates

1155
1156
1157 Randomized studies can be analyzed by straightforward methods without covariates (e.g., chi-
1158 square tests for binary outcomes and t-tests or rank tests for numerical outcomes).
1159 Randomization and significance testing control the probability of a chance imbalance producing
1160 a false positive result for an ineffective drug.
1161

1162
1163 However, methods using covariates may reduce the variability in the estimated treatment effects,
1164 leading to more powerful tests. We recommend choosing covariates in advance on the basis of
1165 their anticipated ability to account for variability in the outcome measure. Post hoc *adjustment*
1166 for imbalances is neither necessary nor desirable, and likely will raise concerns about
1167 multiplicity. In any case, we recommend that variables that may be affected by treatment not be
1168 considered as covariates.

e. Bivariate outcomes

1169
1170
1171 As previously discussed, rescue medication is usually available in opioid analgesic trials. The
1172 interpretation of the results is complicated by this practice. If one group of subjects had less pain
1173 but more use of rescue medication than another, it may not be clear which treatment was better.
1174 We recommend that the protocol specify a way of dealing jointly with pain and rescue. This can
1175 be done in various ways.
1176

1177
1178 A binary outcome can be defined for each individual subject, as discussed in the following
1179 section. The subject should be considered successfully treated if he or she reports a pain score

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1180 less than some prespecified value and takes less than a prespecified amount of rescue
1181 medication. Analysis then proceeds as for any other binary outcome.

1182
1183 By extension, a single numerical score can be assigned to each subject, based on both pain and
1184 rescue medication. It is difficult to define an optimal way of combining these data, but as long as
1185 a method is prespecified, it does not need to be optimal. Any combination of outcomes
1186 indicating improved pain or less rescue use, without a worsening of the other, likely would show
1187 efficacy of the investigational drug (see section IV.B.10.f., Opioid sparing).

1188
1189 Alternatively, multivariate methods can be applied to the aggregate outcomes for pain and for
1190 rescue medication. Again, the choice of such methods need not be shown to be optimal, as long
1191 as it is made in advance and is reasonable.

1192
1193 f. Responder analyses

1194
1195 For some drugs, comparing the change in the mean scores of treatment groups may not be the
1196 best analysis for efficacy. An alternate approach is to compare the number of subjects reaching
1197 prespecified criteria for success (e.g., completing the trial along with showing a certain reduction
1198 in their pain intensity). It is important that a responder analysis incorporate a criterion of
1199 improvement in pain along with criteria for use of rescue medication and other outcome
1200 measures. Sponsors are encouraged to explore the behavior of a variety of outcome measures
1201 and responder definitions during phase 2 to provide a rationale for use of a responder analysis as
1202 primary analysis in phase 3 trials.

1203
1204 g. Multiplicity

1205
1206 As previously mentioned, in addition to the primary assessment of pain intensity and relief, other
1207 assessments of pain and its effect on subjects may be important in fully elucidating the risk-
1208 benefit relationship for the drug. The overall probability of a false positive finding for a
1209 completely ineffective drug is controlled by specifying a single primary analysis. However, if
1210 secondary analyses are intended to support important labeling claims, we recommend
1211 considering the probability of errors in these secondary analyses. We also recommend laying out
1212 a plan in the protocol for controlling them.

1213
1214 **C. Other Considerations**

1215
1216 1. *Risk Management Considerations*

1217
1218 Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) grants the FDA the
1219 authority to require a REMS for certain drug products,²² if we determine that such a strategy is

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.

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1220 necessary to ensure that the benefits of the drug outweigh the risks.²³ We may determine that a
1221 REMS is necessary to support approval of a drug application or may require a REMS after a
1222 drug is approved, on the basis of new safety information.²⁴

1223
1224 We view drug risk management as an iterative process encompassing the assessment of a drug's
1225 risks and benefits, and developing and implementing tools to minimize the risks while preserving
1226 the drug's benefits. It is important in developing any REMS to begin by defining the serious
1227 risks specific to the drug that must be managed. For example, we have determined that a REMS
1228 is required for ER/LA opioid analgesics to mitigate the serious risks of overdose, abuse, and
1229 addiction.

1230
1231 We encourage sponsors to discuss the potential need for a REMS for their analgesic drugs with
1232 the division as early as possible during the clinical development program. If we advise a sponsor
1233 that a REMS is required, the proposed REMS should be complete at the time of submission of
1234 the application. Sponsors should refer to the draft guidance for industry *Format and Content of*
1235 *Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed*
1236 *REMS Modifications* for information on how to format and submit a proposed REMS to the
1237 FDA.²⁵

1238 1239 2. *Skin Studies for Topical Products*

1240
1241 Topical products, either those intended for local drug delivery or those intended to provide
1242 transdermal systemic drug delivery, should be evaluated for dermal toxicity. Topical safety
1243 studies can be most useful if they are conducted with the final to-be-marketed formulation. The
1244 recommended clinical studies are as follows:

- 1245
- 1246 • **Cumulative irritancy studies.** These studies should have at least 30 evaluable subjects.
1247 If sufficient irritation is noted for the drug under study in phase 2 or phase 3 clinical
1248 studies and labeling will include warning regarding the irritation observed, then the
1249 cumulative irritancy study can be waived.
 - 1250
 - 1251 • **Allergenicity (contact allergy) studies.** These studies should have at least 200
1252 evaluable subjects if they are to rule out an incidence of greater than a 1.5 percent
1253 reaction rate.
 - 1254
 - 1255 • **Phototoxicity and photoallergenicity (photo contact allergy) studies.** These studies
1256 can be waived if there is no drug absorbance in the 280 to 700 nM spectrum. The
1257 phototoxicity and photoallergenicity studies also can be waived if the patch²⁶ under study

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

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

²⁵ When final, this guidance will represent the FDA's current thinking on this topic.

²⁶ The dosage form terminology for products that deliver a drug transdermally is currently under discussion between the FDA and the United States Pharmacopeia.

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1258 is opaque or the only indications for use are in areas where there is a minimal chance for
1259 exposure to ultraviolet light.

1260

1261 3. *Fixed-Combination Drug Products*

1262

1263 New fixed-combination drug products composed of two analgesics, such as an NSAID and an
1264 opiate, are expected to be supported in accordance with the FDA’s combination policy
1265 regulations (21 CFR 300.50). This expectation applies to any fixed-combination drug that has
1266 not been previously approved by the FDA (i.e., where the particular active moieties combined
1267 represent a new combination, even if the components have been previously approved separately).
1268 To satisfy 21 CFR 300.50(a), the application for a new combination of two or more analgesic
1269 drug substances must provide data that demonstrate that “each component makes a contribution
1270 to the claimed effects and the dosage of each component (amount, frequency, duration) is such
1271 that the combination is safe and effective for a significant patient population requiring such
1272 concurrent therapy as defined in the labeling for the drug.”

1273

1274 Whereas single-dose studies can demonstrate that the fixed-combination drug product is superior
1275 to the single-ingredient analgesics given alone, this would not ordinarily be a sufficient basis for
1276 approval of the fixed-combination drug product. Even for acute pain indications, it is unlikely
1277 that only single doses of such a fixed-combination drug product would be used. Therefore,
1278 studies that compare the fixed-combination drug product to individual component treatment arms
1279 (+/- placebo) over multiple doses would be expected for such drugs. These multiple-dose studies
1280 would allow for elucidation of the contribution of each component to the claimed effect(s) over
1281 time, would often provide valuable information as to the appropriate patient population (as
1282 referenced in 21 CFR 300.50), and would provide additional safety data to inform the risk-
1283 benefit analysis of any such new combination. Support also should be provided for the choice of
1284 the doses of each individual component in a fixed-combination drug product. Most of the points
1285 made in the previous sections of this guidance apply to new fixed-combination drug products,
1286 but sponsors wishing to develop such drugs are encouraged to meet with the relevant review
1287 division before beginning clinical development to discuss the appropriate clinical program.

1288

1289 4. *CMC Considerations*

1290

1291 Analgesics encompass a variety of dosage forms including solid and liquid oral dosage forms,
1292 transdermal and iontophoretic patches, parenterals, and liquid and semisolid topical
1293 formulations. General guidance pertaining to the CMC of drug development can be found on the
1294 FDA Drugs guidance Web page.²⁷

1295

1296 The usual criteria for developing a dissolution method are applicable and a robust dissolution
1297 method is a necessary tool for assessing in vitro drug release profiles and *abuse deterrent*
1298 properties.²⁸

1299

²⁷ See <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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.

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1300 5. *Specific Labeling Considerations*

1301

1302 a. DESCRIPTION section for transdermal products

1303

1304 For transdermal products, the DESCRIPTION section should include the total drug content of
1305 the transdermal system along with the release rate (in mg per day).

1306

1307 b. Class labeling

1308

1309 Several categories of analgesic drugs have class labeling in one or more sections. For example:

1310

1311 • **NSAID product** labeling includes a boxed warning for risks of cardiovascular
1312 thromboembolic events and gastrointestinal safety. There is also standard language in
1313 other sections of the labeling (e.g., WARNINGS AND PRECAUTIONS) and a class
1314 Medication Guide.

1315

1316 • **ER/LA opioid analgesic product** labeling has a class-wide boxed warning describing
1317 risks associated with Schedule II controlled substances including addiction, abuse, and
1318 misuse that can lead to overdose and death, the risk for life-threatening or fatal
1319 respiratory depression, the risk for fatal overdose following accidental exposure, and the
1320 risk for neonatal opioid withdrawal syndrome in infants born to mothers requiring opioid
1321 therapy while pregnant. There also is standard language for the INDICATIONS AND
1322 USAGE section and for many subsections under WARNINGS AND PRECAUTIONS.

1323

1324 • **Transmucosal oral fentanyl drugs**, as high potency opioids, have consistent language in
1325 much of the product labeling and Medication Guide.

1326

1327 • **Transdermal fentanyl patches** have class labeling for the boxed warning because of
1328 their unique pharmacokinetic characteristics, as well as a standardized Medication Guide.

1329