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# Development of Non-Opioid Analgesics for Acute Pain

## FDA's Draft Guidance for the Industry

**EXCUTIVE SUMMARY**

- In February 2022, the U.S. Food and Drug Administration (FDA) issued draft guidance for the development of **non-opioid analgesics for acute pain**.

- This guidance was in response to requirements in a **recently passed Act**, the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act. Specifically, Section 3001(b) in the Act.

- This Act **directs the FDA** to issue guidance to help address challenges to developing non-addictive medical products to manage pain.

- In keeping with the mandate of Section 3001(b), and considering the severity of the ongoing opioid crisis, this guidance is also intended to **assist industry sponsors** in the development of alternatives to opioids for the management of acute pain.

- Accordingly, the FDA's guidance addresses its current thinking about three specific topics: (1) development of **non-opioid** analgesic products for **acute pain**
  (2) **labeling** claims
  (3) **expedited programs** as they pertain to this purpose

- "Analgesics, also called "**painkillers"** are medications that relieve different types of pain – from headaches to injuries to arthritis.

- Anti-inflammatory analgesics **reduce inflammation.**

- Opioid analgesics change the way the "**brain perceives pain**".

 

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**BACKGROUND**

- The FDA is committed to using its authorities to take measures to combat the opioid crisis. In 2017, the FDA announced its intention to focus on four priorities, two of which directly relate to this guidance:
  (1) fostering the **development** of novel analgesic drugs
  (2) decreasing opioid analgesic exposure and **preventing new addiction.**

- For the purposes of this FDA guidance, acute pain is defined as pain, **lasting up to 30 days**, typically in response to some form of tissue injury, such as trauma or surgery. Acute Pain is generally accepted as being of recent onset and **limited short duration**. It usually follows immediately after surgery/trauma and causal (has a known cause) relationship to injury or disease.

- The intensity of acute **pain is greatest** at the onset of injury, but with healing, pain intensity reduces.

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

**DEVELOPMENT OF NON-OPIOID ANALGESICS FOR ACUTE PAIN**

## 1. General Considerations

Some sponsors may initially choose to demonstrate effectiveness of a particular drug in a **specific pain-type population,** and then subsequently, pursue additional specific indications, for a general indication, with **additional trials** in other acute pain settings to support broader use.

In both of these scenarios, additional patient populations and types of pain can be studied and study results submitted as efficacy supplements to broaden the indication. In many cases, for both additional specific indications or to expand the indication from a specific pain indication to a general indication, one additional adequate and well-controlled efficacy **trial may be sufficient**.

## 2. Trial Design

 

- Clinical trials to support a finding of efficacy for a non-opioid analgesic should be **randomized, double-blind, superiority trials**. The trials should include repeat-dose design as appropriate.

- Treatment duration should be based on the pain model used to support the proposed indication sought but should be **no fewer than 24 hours** for products that are not limited to a single dose.

- The primary endpoint should be based on the change in pain intensity over a suitable time based on the pain model used in the trial and the **product's expected** duration of pain relief; however, the time period assessed does not have to be for the full duration of the pain.

- After evaluation of the primary endpoint, we recommend continued evaluation of both **safety and efficacy**, for evidence of sustained effect, which may be relevant to acute pain lasting up to 30 days.

## 3. Outcome Measures to Obtain an Acute Pain Analgesic Indication

#### PRIMARY EFFICACY ENDPOINT

- In general, an assessment of pain intensity is the **primary outcome measure** to establish the efficacy of an analgesic intended to manage acute pain.

- Efficacy endpoints (e.g., change in pain intensity) in a non-opioid analgesic trial should reflect a **direct rating of pain intensity** by the subject for all settings in which the subject can communicate in a reliable manner.

#### SECONDARY EFFICACY ENDPOINTS

- Secondary outcome measures are important to **fully characterize the efficacy** of a non-opioid analgesic and should support the primary efficacy endpoint. These secondary outcome measures include the measurement of time to onset of pain relief and time to rescue or request for next dose of the study drug.

- Other informative secondary outcome measures include assessment of use of rescue medications, physical function, and patient global impression of change of pain.

 

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## 4. Safety Considerations

- Appropriate assessment of both **effectiveness and safety** relies on accurate and complete capture of the reason for subject discontinuation. Sponsors should assure that when a subject discontinues study drug or withdraws from the trial that **the specific reason** is obtained.

- Investigators should be prompted to provide detailed information, with **specific causes** rather than report terms such as "other," "subject request," "investigator decision," or other such nonspecific categories.

- Industry sponsors also should ensure that case report forms are designed to accurately **capture the reason** for patient discontinuation.

SOURCES: U.S. FOOD & DRUG ADMINISTRATION, ALLEN RESEARCH ENDOWMENT, INC., CLEVELAND CLINIC