Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework

Guidance for Industry

DRAFT GUIDANCE

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

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I. INTRODUCTION

The purpose of this guidance is to describe the benefit-risk assessment framework that the Agency uses in evaluating whether applications for opioid analgesic drugs meet the standard for approval under section 505 of the Federal Food, Drug, and Cosmetic Act. This guidance summarizes the information that should be included in a new drug application for an opioid analgesic drug to facilitate the Agency's benefit-risk assessment.

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

II. BACKGROUND

Benefit-risk assessment is the foundation for FDA's regulatory review of human drugs and biologics. These assessments capture the evidence, uncertainties, and reasoning used by FDA to arrive at its regulatory decisions. Additionally, these assessments serve as tools for communicating that information to those interested in a better understanding of FDA's thinking.

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

FDA has developed a benefit-risk assessment framework — a structured, qualitative approach to FDA's benefit-risk assessment[2] formatted as a table (see Figure 1 below).[3] In Figure 1, the factors affecting the benefit-risk assessment are listed on the left side. As reflected in the shaded boxes, the top two factors (*Analysis of Condition* and *Current Treatment Options*) relate to the specific therapeutic area — the current state of knowledge regarding the condition to be treated and the available therapies. The bottom two factors (*Benefit* and *Risk and Risk Management*) are specific to the drug at issue.

FDA assesses risks and benefits of all drugs in the context of the use indicated in the labeling. However, because of the widespread misuse and abuse of prescription opioid analgesic drugs, for this class of drugs, FDA also considers the broader public health effect of opioid analgesic drugs; this involves consideration of the risks related to misuse, abuse, opioid use disorder, accidental exposure, and overdose, for both patients and others. Likewise, FDA considers any properties of a drug expected to mitigate these risks. This guidance describes the various factors that FDA will consider in evaluating the benefits and risks of an opioid analgesic drug. FDA encourages applicants to provide information relevant to these factors.

Figure 1: FDA's Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment		
Benefit-Risk Dimensions		
Dimension	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk and Risk* Management		

* For purposes of this figure, *Risk and Risk Management* includes not only risks to the patient when used as indicated but also risks related to the broader public health sometimes described as second-order effects. And, in assessing risks to the broader public health, the Agency is making an assessment relative to other currently available analgesic drugs.

[2] See the Enhancing Benefit-Risk Assessment in Regulatory Decision-Making web page available at https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm.

[3] See the Benefit-Risk Assessment in Drug Regulatory Decision-Making implementation plan available at https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM602885.pdf.

III. BENEFIT-RISK ASSESSMENT

The following sections describe the information that FDA will consider in assessing the benefits and risks of an opioid analgesic drug. Consistent with the benefit-risk assessment framework, FDA considers the benefits and risks to the patient when the drug is used as labeled, as well as the benefits and risks relative to other available therapies for pain. Additionally, FDA considers the public health risks of the drug related to misuse, abuse, opioid use disorder, accidental exposure, and overdose in both patients and nonpatients, as well as any properties of the drug that may mitigate such risks. Note that the risk of opioid use disorder can arise even when a patient is taking an opioid analgesic drug as labeled.

The sections below provide recommendations for information the applicant should provide to assist FDA in its assessment.

A. Benefits to the Patient Using the Drug as Labeled

The Agency will consider questions including the following about benefits to patients who are prescribed the drug and take it as labeled and directed by their prescribers:

- Analgesic efficacy of the drug when used for its proposed indication
  - What is the body of evidence supporting a finding of analgesic drug efficacy?
  - In what patient population(s) was efficacy demonstrated? Why was the patient population chosen for the efficacy study? How does the population studied reflect the proposed indication (i.e., is the proposed indication broader than the population studied)?
  - What is the body of evidence supporting the proposed duration of use for each proposed indication?
- Safety of the drug when used for its proposed indication
  - Does the drug have characteristics that mitigate adverse events associated with opioid analgesic drugs, including respiratory depression, sedation, and constipation? What data support the conclusion that these risks are mitigated?
  - Does the drug have characteristics that mitigate the risk of opioid use disorder when used as labeled? How do the safety data support this?

B. Risks to the Patient Using the Drug as Labeled

In addition to the already known risks associated with opioid analgesic drugs, the Agency will also consider questions including the following about risks to patients who are prescribed this drug and take it as labeled and directed by their prescribers:

- Does this particular drug have any novel risks not typically associated with opioid analgesic drugs? How serious are they? Can they be mitigated through monitoring, patient selection characteristics, or limiting duration of use? Are the novel risks reversible?

- Do the formulation and/or excipients pose risks to patients (e.g., tablets that swell in the gastrointestinal tract, tablets that may adhere to moist mucosal surfaces)? For drugs formulated to have abuse-deterrent properties, are there any adverse events associated with the drug product when used as labeled that are attributable to aversive excipients or excipients intended to impart resistance to manipulation?

- Are there characteristics of the drug that increase or decrease the risk for respiratory depression, sedation, or development of opioid use disorder in patients (e.g., large residual opioid in transdermal systems, high dosage strengths)? Can the risks be mitigated by particular packaging configurations or storage and disposal conditions?

- Is there evidence that adverse events typically associated with opioid analgesic drugs occur at a higher rate or with greater severity with the new drug than expected for similar drugs based on clinical trials or theoretical risks?

C. Effectiveness and Safety Relative to Approved Analgesic Drugs

As part of the benefit-risk assessment for a particular drug and proposed indication, FDA considers the benefits and risks relative to other available therapies for the condition. FDA will consider the questions including the following in assessing effectiveness and safety of an opioid analgesic drug:

- Do any comparative efficacy data exist for the drug relative to approved opioid or nonopioid analgesic drugs? Does this analgesic drug offer any advantages relative to available approved analgesic drugs for each indication, with regard to effectiveness or duration of response?

- Do any comparative safety data exist for the drug relative to approved opioid or nonopioid analgesic drugs? Does this analgesic drug offer any other safety advantages or disadvantages relative to available approved analgesic drugs for each indication (e.g., abuse-deterrent properties, less risk of drug-drug interactions)?

- What is the anticipated benefit-risk balance relative to available approved analgesic drugs for each indication? Do any comparative safety data exist for the drug relative to approved opioid or nonopioid analgesic drugs? Does this analgesic drug offer any other safety advantages or disadvantages relative to available approved analgesic drugs for each indication (e.g., less risk of drug-drug interactions)?

- Does the drug have any other advantages over other available approved analgesic drugs (e.g., can be mixed with food)?

FDA notes that, while the comparative data described above is helpful in applying the benefit-risk framework, superiority to other available treatments is not a requirement for approval under FDA's drug approval authorities.

D. Broader Public Health Effects: Risks and Mitigation of Risks Related to Misuse, Abuse, Opioid Use Disorder, Accidental Exposures, and Overdose

In the overall benefit-risk assessment of opioid analgesic drugs, FDA will consider the positive and negative public health effects of the drug, which includes the drug's potential effect on risks to both patients and nonpatients, such as members of the patient's household (e.g., children, teenagers, visitors, and others). The risks considered include those related to misuse, abuse, opioid use disorder, accidental exposure, and overdose. FDA's evaluation of the broader public health effect of a new opioid analgesic drug is made relative to other currently available analgesic drugs.

- In evaluating ways in which an opioid analgesic drug positively or negatively affects public health FDA will consider the following:

  - Are there characteristics of the drug that increase or decrease the risk of accidental exposure in children (e.g., tablet size, color, flavor, packaging configuration, appearance of topical systems)?

  - Are there characteristics of the drug that increase or decrease the risk of misuse, abuse, opioid use disorder, and related adverse outcomes such as overdose and infectious complications of injection (e.g., abuse-deterrent properties, large residual opioid in transdermal systems, high dosage strengths)? Can the risks be mitigated by particular packaging configurations or storage and disposal conditions?

  - Are there increased or decreased risks associated with the indicated method of delivery (i.e., delivery device)? For example, does the delivery method affect an existing risk or introduce a novel risk?

  - To support the opioid-specific public health benefit-risk evaluation, the applicant should use traditional epidemiologic data sources (e.g., surveys, emergency department visits, poison control center calls) and nontraditional sources (e.g., internet discussion forums and blogs, social media, qualitative/ethnographic studies, law enforcement data) to provide information about how this moiety or similar opioid analgesic drugs are misused and abused in postmarketing settings. These data should address demographic patterns of abuse, the routes by which these drugs are abused, concomitant abuse of other substances, as well as risks of related adverse outcomes (e.g., addiction, fatal and nonfatal overdose, infectious complications of abuse).

- For abuse-deterrent formulations, in addition to considering any potential benefits of such drug products, FDA also will consider the following in terms of opioid-specific public health considerations:

- Potential unintended adverse consequences with introduction of the abuse-deterrent formulation, such as the following:

  - A shift to more dangerous routes of abuse (e.g., nasal to the more dangerous intravenous) based on properties of the formulation.

  - Potential tampering methods that could result in harmful effects, including injection-related harms (e.g., large volume extraction of drug that leads to increased sharing of drug paraphernalia increasing the risk of human immunodeficiency virus and hepatitis transmission).

  - Any other potential safety concerns related to the abuse-deterrent formulation.

- For safety of excipients by unintended routes of administration, FDA will consider the following in terms of opioid-specific public health considerations:

  - Based on a risk assessment of the excipients in the drug, the potential safety concerns for the drug when administered by unintended routes of administration, including intravenous, intranasal, and inhalation.

- For specific populations that may present distinct benefit-risk profiles, FDA will consider the following in terms of opioid-specific public health considerations:

  - The potential for subpopulations where the benefit-risk balance may be unfavorable (e.g., adolescents, patients with mental health and/or substance use disorders, patients with certain other comorbidities). The applicant should include a discussion of anticipated use-specific subpopulations and proposed approaches to mitigate such risks, if present.

E. Risk Management

FDA has determined that a class-wide risk evaluation and mitigation strategy (REMS) is necessary for all opioid analgesic drugs intended for outpatient use to ensure that the benefits of these drugs continue to outweigh the risks.[4] The Opioid Analgesic REMS program requires that training be made available to all health care providers (HCPs) who are involved in the management of patients with pain, including nurses and pharmacists.[5] To meet this requirement, drug companies with approved opioid analgesic drugs provide unrestricted grants to accredited continuing education providers for the development of education courses for HCPs based on

[4] See the Opioid Analgesic Risk Evaluation and Mitigation Strategy web page at https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm. Note that certain opioid analgesic drugs are subject to other REMS. Information on the specific REMS associated with each approved opioid analgesic drug can be found on the FDA's Approved Risk Evaluation and Mitigation Strategies (REMS) web page at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm.

[5] Ibid.

FDA's Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain.[6]

To the extent that the safety profile of a drug product may differ from those drug products covered by the class-wide REMS, a product-specific REMS or REMS element may be required. For example, an opioid analgesic drug that must be restricted to use in a monitored inpatient setting may need additional risk mitigation strategies to ensure the drug product does not leave the hospital. In short, the applicant for an opioid analgesic drug should include any proposed REMS that the applicant considers necessary to ensure a drug's benefits outweigh its risks. All sponsors of opioid analgesic drugs should begin discussions with FDA early during drug development regarding product-specific risks and the potential need for additional risk mitigation.

[6] Available at https://www.accessdata.fda.gov/drugsatfda_docs/rems/Opioid_analgesic_2018_09_18_FDA_Blueprint.pdf.