Opioid Use Disorder: Developing Depot Buprenorphine Products for Treatment

Guidance for Industry

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

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Contains Nonbinding Recommendations

Opioid Use Disorder: Developing Depot Buprenorphine Products for Treatment Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance reflects the Agency's current thinking regarding drug product development and trial design issues relevant to the study of depot buprenorphine products (i.e., modified-release products for injection or implantation) for the treatment of opioid use disorder (OUD). This guidance focuses on the development of depot buprenorphine products for which submission of a new drug application (NDA) through the pathway described in section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) may be appropriate.[2]

For recommendations on specific depot buprenorphine product development programs, sponsors should contact the Division of Anesthesia, Analgesia, and Addiction Products (the Division) in the Center for Drug Evaluation and Research.

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.

[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.

[2] The 505(b)(2) pathway is appropriate for applications that contain full reports of investigations of safety and effectiveness, where at least some of the information required for approval is derived from studies that are not conducted by or for the applicant and for which the applicant has not obtained a right of reference. Such investigations or information can include, for example, FDA's finding of safety and/or efficacy for a listed drug or published literature. NDAs submitted through the 505(b)(2) pathway may be subject to patent certification requirements and periods of exclusivity that could affect approval. See generally 505(b)(2) of the FD&C Act; see also the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999). 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 guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

II. BACKGROUND

Buprenorphine, at sufficient plasma exposures, can block the effects of exogenous opioids and, at lower plasma exposures, may be sufficient for maintaining patients who have achieved sustained clinical stability on other buprenorphine therapies. Passive-compliance formulations such as sustained-release injectable depots and implants can provide effective treatment of OUD in a treatment paradigm that may be less subject to misuse, abuse, or accidental exposure compared to self-administered formulations such as transmucosal tablets and films.

III. DEVELOPMENT PROGRAMS

In general, an application for a depot buprenorphine product can be submitted through an abbreviated new drug application (ANDA) under section 505(j) or an NDA under section 505(b)(2) of the FD&C Act.[3] The regulatory pathway and the need for additional studies depend on the characteristics of the investigational depot buprenorphine product (e.g., delivery system, formulation) relative to an approved buprenorphine product.[4] For example, an investigational monthly subcutaneous depot buprenorphine product that does not meet criteria for submission under an ANDA may be submitted under a 505(b)(2) NDA with relative bioavailability pharmacokinetic studies and may not require additional efficacy and/or safety studies in certain instances.[5] Applications for other investigational depot buprenorphine products with novel features could also be eligible for submission through the 505(b)(2) pathway, but may require efficacy and/or safety trials.

A. Types of Studies to Support Approval

1. Depot Buprenorphine Products That Are Similar to an Approved Depot Product

For new depot buprenorphine products that could be submitted under a 505(b)(2) NDA, new efficacy trials may not be necessary, and a sponsor may be able to rely on the Agency's previous findings of safety and/or efficacy for an approved depot buprenorphine formulation using relative bioavailability pharmacokinetic studies.

The final to-be-marketed drug product (including drug delivery component and formulation) and the dosing regimen proposed for inclusion in the drug product labeling should be used in the pharmacokinetic studies and clinical trials to support approval. If a drug product other than the

[3] Although it is not the focus of this guidance, applicants can also submit an NDA for a depot buprenorphine product through the 505(b)(1) pathway for which the application contains full reports of investigations of safety and effectiveness that were conducted by or for the applicant or for which the applicant has a right of reference. See section 505(b)(1) of the FD&C Act.

[4] Under these abbreviated approval pathways, in general, an applicant can rely on FDA's finding of safety and effectiveness for a drug product approved under section 505(c) of the FD&C Act. For brevity, the remainder of this guidance refers to an approved drug product generally without reference to the legal pathway for approval.

[5] See the draft guidance for industry *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (October 2017). When final, this guidance will represent the FDA's current thinking on this topic.

final to-be-marketed drug product is used, the sponsor should provide additional bridging information or justification to address the difference.

In determining whether a sponsor needs to conduct efficacy trial(s) of an investigational depot buprenorphine product, key comparative parameters between the investigational depot buprenorphine product and an approved depot buprenorphine product include the degree of similarity in the following:

- The shape of the pharmacokinetic profile
- The time to reach a plasma level associated with blockade of exogenous opioids[6]
- The maximum plasma concentration
- The minimum (trough) plasma concentration
- The plateau buprenorphine concentration following the initial peak after the first depot injection
- Accumulation after multiple doses
- Estimated time for complete clearance of the drug product after steady state has been reached

If these parameters are sufficiently similar to the approved depot buprenorphine product, efficacy trials would not need to be conducted because the sponsor of the investigational depot buprenorphine product could typically rely for approval on the Agency's findings of safety and efficacy for the approved depot buprenorphine product. Sponsors should include the following elements in the development program for such depot buprenorphine products:

- Human-factors engineering processes should be utilized throughout development of the depot buprenorphine product. For example, the sponsor should develop and test training materials for insertion and removal of the depot buprenorphine product, if applicable.
- Comparative bioavailability pharmacokinetic studies should demonstrate that exposure to the investigational depot buprenorphine product is similar to that of an approved depot buprenorphine product both after single dose and at steady state following multiple doses.
- The safety of any new excipients or materials should be demonstrated.

[6] Comparison of partial areas under the curve may be a useful method of assessment.

2. Depot Buprenorphine Products With Novel Features Relative to Approved Depot Products

A sponsor could likely submit an investigational depot buprenorphine product with novel features relative to approved buprenorphine products (e.g., dosing interval, dose range, route of administration) under a 505(b)(2) NDA, but an efficacy trial and/or safety study may be needed. To ensure that any necessary efficacy trials and/or safety studies are designed based on relevant information specific to the investigational depot buprenorphine product, the development program for such depot buprenorphine product should proceed in a sequential fashion, as follows:

- The sponsor should determine the target plasma concentration. The sponsor can use receptor occupancy studies, literature, or other sources of information for this determination.

- The sponsor should perform initial pharmacokinetic studies to identify doses or regimens that deliver the target plasma concentration during the desired treatment period, including any appropriate comparisons to an approved depot buprenorphine product as described in section III. A. 1., Depot Buprenorphine Products That Are Similar to an Approved Depot Product.

- The sponsor should provide human behavioral pharmacology data to identify doses in nontreatment seeking trial subjects (a *blockade trial*). This trial should establish that the investigational depot buprenorphine product blocks completely (i.e., not merely attenuates) the subjective responses to a clinically relevant dose of an exogenous opioid.

- The sponsor should consider human-factor issues related to the procedures necessary to administer the investigational depot buprenorphine product during the entire development program. If a surgical procedure is required, the sponsor should develop and test appropriate training materials for methods of insertion and, if applicable, removal.

- If the investigational buprenorphine product dosing, including interdose interval and timing of treatment initiation (e.g., with respect to the last time of abused drug use, need for initial treatment with a transmucosal buprenorphine product), is significantly different from that of an approved buprenorphine product, the efficacy of the investigational depot buprenorphine product should be demonstrated in at least one adequate and well-controlled clinical trial.

- Studies may be needed to show the safety of the investigational depot buprenorphine product (e.g., if using a novel drug product delivery component or route). If an independent efficacy trial is needed, the safety data from this trial may satisfy part or all the safety study requirement, after preliminary human safety testing is done. Otherwise, the sponsor can study human safety independently, along with a strategy for mitigating any risks identified.

B. Efficacy Trials

1. Trial Design

When a sponsor needs to conduct efficacy trial(s), it should include the following elements:

- The trial should be a blinded, controlled trial studying the doses or regimens established as blocking in the blockade trial.

- Controls should include placebo or an approved formulation of buprenorphine product. Active-controlled trials can employ either superiority or noninferiority designs. Sponsors should consult the Division regarding different aspects of trial design, including the noninferiority margin.

- All trials, particularly those with placebo, should include in the protocol careful monitoring for clinical worsening or relapse and provisions for rescue treatment or removal of the patient from the trial with transfer to standard of care.

- The characteristics of patients enrolled in the trial should reflect the intended use of the investigational depot buprenorphine product including the following:

  - Patients should meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-5) criteria for moderate-severe OUD.

  - For use as initial therapy, patients should be new entrants to treatment (i.e., actively ill and not currently receiving other drug product treatments for OUD). A history of previous drug product treatments for OUD is acceptable.

  - Sponsors can conduct trials in patients already stable on other treatments. Such trials, if appropriately designed, would support a claim of reduction in risk of relapse but would not support a claim of efficacy in new entrants to treatment.

  - Patients should be either new entrants to treatment or stable on other treatments. Trials in a heterogeneous population of new and stable patients present significant barriers to interpretation and, therefore, are much less likely to demonstrate efficacy.

- The sponsor can employ an initial titration period using an approved transmucosal buprenorphine product formulation if this is the intended regimen for transitioning to the investigational depot buprenorphine product. Similarly, the sponsor can employ a period of stabilization with a transmucosal formulation if this is anticipated to be part of the intended regimen for the investigational depot buprenorphine product.

- Patients should be seen at least weekly and assessed for the following:

  - Safety, including injection or implantation site reactions

- Clinical response, including urine toxicology screen for opioid and other abused drug use, self-report of drug use, and measures of clinical benefit or function

- Attempts to remove the investigational drug product

2. Recommended Efficacy Endpoints

FDA's recommended primary efficacy endpoint is a decrease (for superiority trials) or noninferiority (for active-controlled trials) in use of opioids.

- A sponsor should consider the following when developing a responder definition:

  - The responder definition should be appropriate to the schedule of assessments. The sponsor should consider the pharmacokinetic and pharmacodynamic profiles of the investigational depot buprenorphine product in determining the frequency of sampling to evaluate clinical response. The definition of a responder depends, in part, on the frequency of sampling.

  - If the sampling for toxicology screen is frequent enough to capture every opioid use, a negative assessment at all sampling visits (*complete abstinence*) is not necessary to define a clinical responder. However, as the interval between sampling is increased, the ability to detect opioid use decreases, and the absence of positive assessments becomes more critical to the responder definition.

  - The following are other principles sponsors should follow when developing a responder definition:

    - Noncompleters should be adjudicated as nonresponders

    - For superiority comparisons, missing values for illicit or unauthorized drug use should be imputed as positive. Note that this approach could bias the results toward no treatment difference achieving noninferiority even when the investigational drug product is inferior.[7]

    - A grace period can be included. A *grace period* is a predefined period of time during which the abused drug use information is not incorporated into the efficacy assessment. It may be appropriate to allow patients time for engagement in treatment because patients entering treatment may not respond immediately.

[7] For approaches to address this bias in noninferiority comparisons, refer to the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

- Efficacy analyses should include the following:

  - Comparison of responder rates
  - Cumulative responder curves[8]
  - Graphic displays of individual patient responses

For recommendations on the adequacy of the responder definition and additional analyses for specific depot buprenorphine product development programs, sponsors should contact the Division.

3. Novel Efficacy Endpoints

Sponsors can also propose novel efficacy endpoints (e.g., reduction in *craving*, improvement in sleep or mood, other patient-reported outcomes) that are not focused on opioid and other abused drug use assessed by toxicological testing. To assess efficacy the sponsor should appropriately support these novel endpoints with data demonstrating the ability of the endpoints to identify a clinically meaningful benefit. Currently, such endpoints are not well supported by publicly available data. Additional research is needed to explore and better define instruments to measure these patient-reported outcomes[9] in trials. If a sponsor plans to include novel endpoints in a depot buprenorphine product development program, FDA strongly encourages the sponsor to discuss such plans with the Division early in the drug product development process.

There is great public heath interest in assessing additional, clinically meaningful endpoints such as reduction in hospitalizations, emergency department visits, overdose, and death, as well as improvements in the ability to resume work, school, or other productive activity. Though understanding these outcomes would be highly valuable, the Agency recognizes that evaluating these outcomes could require larger trials than those usually conducted for marketing approval. However, use of such endpoints could provide the basis for additional claims for approved buprenorphine products.

[8] A *cumulative responder curve* or *cumulative distribution function* refers to an approach in which various possible definitions of *responder* are considered and compared graphically. The graph shows, for example, the percentage of patients who provided a given percentage of negative samples or better. Therefore, the curves fall from 100 percent at the left to zero percent at the right.

[9] See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009).