Development of Local Anesthetic Drug Products With Prolonged Duration of Effect

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DRAFT GUIDANCE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)

March 2023
Clinical/Medical

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Development of Local Anesthetic Drug Products With Prolonged Duration of Effect Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors that are developing local anesthetic drug products to produce postoperative analgesia for a prolonged duration, for which submission of a new drug application (NDA) through the pathway described in section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) is appropriate. This guidance is not applicable to applications that meet criteria for submission under section 505(j) of the FD&C Act, petitioned abbreviated new drug applications under section 505(j)(2)(C) of the FD&C Act, or applications submitted under section 351 of the Public Health Service Act.[2]

For assistance with specific local anesthetic drug product development programs, sponsors should contact the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (the Division) in the Office of New Drugs in the Center for Drug Evaluation and Research.[3]

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 Anesthesiology, Addiction Medicine, and Pain Medicine in the Office of New Drugs in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] See the guidance for industry *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (May 2019). 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/regulatory-information/search-fda-guidance-documents.

[3] For the purposes of this guidance, the term *sponsor* will be used to refer to both sponsors of investigational new drug applications and applicants of NDAs.

II. BACKGROUND

Local anesthetic drug products may be used to either reduce painful sensations (i.e., provide analgesia) or to completely eliminate sensation (i.e., provide anesthesia). The administration of these drug products has been used to reduce or eliminate the pain associated with many surgical procedures, such as inguinal hernia repair or total knee arthroplasty.

Local anesthetic drug products are administered in a number of ways, including subcutaneous injection, wound instillation or smear, perineural infiltration (e.g., peripheral nerve block), fascial plane blocks (i.e., transverse abdominis plane block), or via the neuraxial administration (i.e., epidural, intrathecal). Although there may be other modes of administration (e.g., deep sympathetic block) utilized for chronic pain etiologies, this guidance only focuses on methods of administration targeted to provide postoperative analgesia.

Local anesthetic drug products include those that have a single active ingredient or multiple active ingredients, such as a local anesthetic in combination with a vasoconstrictor (e.g., epinephrine). Additionally, local anesthetic drug products may be immediate-release products or modified-release products (e.g., extended-release injectable suspension). In addition, local anesthetic drug products can be administered using various types of devices. Although different local anesthetic drug products have different pharmacokinetic (PK) profiles, in general their effects last a few hours. However, the increasing interest in reducing or eliminating the use of opioid analgesic drug products is leading to development of dosage forms of local anesthetic drug products that prolong the duration of action of the drug product to a period of days rather than hours.

In addition, some local anesthetic drug product dosage forms may be drug-device combination products as defined under 21 CFR 3.2(e).[4] For example, the local anesthetic may be embedded or otherwise contained in an implant that controls the rate of drug release/delivery to the surrounding tissues. In this context the anesthetic drug would be the drug constituent part and the implant would be the device constituent part of the combination product.[5, 6] Other combination product examples include a local anesthetic drug-prefilled syringe or a copackage of a local anesthetic drug in a vial and a software-controlled delivery device.

III. DEVELOPMENT PROGRAMS

The development program of a local anesthetic drug product with prolonged duration of effect will depend, in part, on the intended use, such as anesthesia, analgesia, or both, and whether the drug substance has already been approved in a drug product or if it is a new drug substance. This

[4] For general information on combination products, see the Combination Products: Guidance and Regulatory Information web page at http://www.fda.gov/combination-products/guidance-regulatory-information.

[5] See 21 CFR 4.2 for the definition of *constituent part*. For purposes of this guidance, the terms *device* and *device constituent part* are used interchangeably.

[6] For purposes of this guidance, the terms *drug*, *drug product*, and *drug constituent part* are interchangeable. Also, the term *product* applies to the to-be-marketed drug product or combination product.

guidance focuses on development programs for local anesthetic drug products for the indication of postoperative analgesia.

For a new dosage form or a new formulation of a previously approved dosage form of an approved local anesthetic drug product, the NDA can be submitted as a stand-alone application (i.e., 505(b)(1)) or pursuant to section 505(b)(2) of the FD&C Act.[7] For drug products submitted as stand-alone applications, sponsors should plan to provide data and/or conduct studies that establish the efficacy and safety of the drug product as a local anesthetic drug product, in addition to supporting the safety and efficacy of the formulation. For drug products submitted under section 505(b)(2), the number and type of studies necessary to support approval of the drug product will depend on the proposed indication, proposed dosage and administration, the known safety and efficacy profile of the previously approved local anesthetic drug product (i.e., listed drug), drug product composition, and other characteristics of the proposed drug product (e.g., in vitro drug release profile, delivery device, formulation) relative to the listed drug.[8]

Sponsors should discuss their development plans with the Division early in development, including, but not limited to, planned comparative bioavailability studies and efficacy and safety studies. Efficacy and safety studies will be necessary to support drug products that are the first modified-release formulation for any existing immediate-release local anesthetic drug product or that have significant differences (e.g., in PK profile) from approved drug products.

To ensure that the necessary efficacy and/or safety studies are adequately designed and include the relevant information specific to the proposed local anesthetic drug product, the development program for the local anesthetic drug product should proceed in a sequential fashion, as follows:

- Sponsors should conduct in vitro studies to characterize drug release profile. Based on the proposed formulation, the type and design of these studies should be discussed with the Division early on in the development program.

- Sponsors should conduct initial PK studies to identify doses and dosing regimens that deliver target PK and pharmacodynamic (PD) profiles during the desired treatment

[7] Although applications submitted as stand-alone applications are not the focus of this guidance, a sponsor can submit an NDA for an extended-release local anesthetic drug product as a stand-alone application when 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. 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 were 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 section 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/regulatory-information/search-fda-guidance-documents.

[8] Under these abbreviated approval pathways, generally 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.

period, including PK parameters described in section III.A., General Clinical Pharmacology Considerations.

- Sponsors should conduct safety and efficacy studies designed to support the proposed indication. The number, type, and design of these studies should be discussed with the Division and will be based on multiple considerations, including if the proposed local anesthetic drug product:

  — Is the first modified-release formulation for an existing immediate-release local anesthetic drug product (i.e., has no previously approved modified-release formulation) and is being compared to the immediate-release formulation of the proposed local anesthetic drug product.

  — Has significant differences compared to the listed drug, namely the following:

    - The in vitro data, such as drug release profile, for the proposed local anesthetic drug product differs significantly from the listed drug.

    - The proposed local anesthetic drug product has novel features, such as the following:

      i. Dosing, including timing interval of repeated doses, dose range, route of administration, etc., relative to the listed drug.

      ii. A novel device constituent part or excipient that facilitates drug delivery. In this case, if an independent efficacy trial is conducted, the safety data from this trial may satisfy part or all of the safety evaluation requirements.

A. General Clinical Pharmacology Considerations

For the purposes of this guidance, the term *pharmacokinetics* refers to systemic drug exposure, unless noted otherwise. When characterizing the PK profile of a local anesthetic drug product, sponsors should consider and/or address the following concepts:

- Due to the method(s) of administration of these products, it may be challenging to measure local drug concentrations and characterize PK profile for local drug exposure. If the sponsor plans to collect PK samples for local drug exposure and characterize the PK profile, the sponsor should propose a reliable methodology or approach to accurately measure local drug concentrations and discuss the proposal with the Division early in development.

- The PK profile may differ at various sites of administration and may depend on total dose, method of administration, and the vascularity of the anatomical site.

- The sponsor should characterize the PK profile for every anatomic site/route(s) of administration that the sponsor proposes to include in drug product labeling. If the

sponsor is seeking a broad postsurgical indication for administration of the proposed drug product at any anatomical surgical site, the sponsor should demonstrate the predictability of the PK profile for different anatomic sites and routes of administration or provide justification on how data can be extrapolated to additional, nonstudied, sites.

- The sponsor should use maximum systemic exposure at the highest dose, via the proposed route of administration to assess safety; however, systemic exposure does not typically correlate with efficacy for local anesthetic drug products.

- The sponsor should consider the time for complete clearance of the drug product after last administration to delineate the duration of systemic safety monitoring and determine the appropriate timing for additional dose(s) of local anesthetic drug products.

For any proposed local anesthetic drug product, the sponsor should obtain the following key PK parameters:

- The shape of the PK profile
- The time to reach maximum plasma concentration (T_{max})
- The maximum plasma concentration (C_{max})
- The extent of systemic exposure (AUC)
- The minimum (trough) plasma concentration (C_{trough})
- Accumulation after multiple doses, if applicable
- Estimated time for complete clearance of the drug product after last administration

Although demonstrating there are no clinically significant differences in the pharmacokinetics of systemic drug exposure, including AUC and C_{max}, compared to another approved drug product with prolonged duration of effect could potentially support approval, additional efficacy and safety studies may be necessary for the following reasons:

- Product composition will likely vary between different local anesthetic drug products, which may affect local safety as well as local efficacy of the drug product.

- In vitro release characteristics may vary based on drug product formulation, which may affect local drug exposure, even if there are no clinically significant differences in systemic drug absorption.

- The rate of systemic absorption of local anesthetic drug products may also vary based on the total dose of drug product administered, the route of administration, and the vascularity of the administration site. Therefore, comparable AUC and C_{max} does not necessarily mean that the shape of the PK profiles of the two drug products are comparable.

- Comparable levels of systemic exposure (i.e., systemic pharmacokinetics) between two different drug products may not reflect comparable local drug concentration at the same site of administration.

- Because local drug concentrations do not necessarily correlate with systemic exposure, it is unlikely that comparable local efficacy can be demonstrated.

If a sponsor decides to conduct only relative bioavailability PK studies with the proposed local anesthetic drug product and to rely on the Agency's findings of safety and/or efficacy for the listed drug, the following data may be necessary:

- Comparative in vitro data, such as drug product composition, formulation characteristics (e.g., liposome characteristics), in vitro release characteristics, etc. The sponsor may use available in vitro data to inform in vivo PK characteristics of the drug product.

- Comparative bioavailability PK studies that demonstrate that local and systemic exposure to the proposed local anesthetic drug product is similar to that of the listed drug after single dose administration and following multiple doses of the same drug product.

- Data to assess the impact of the differences in the proposed formulation, in vitro characteristics, dosing and administration, etc., on local drug exposure, and consequentially local safety and local efficacy.

If clinical studies are not needed to support efficacy and safety (local and systemic safety) of the proposed local anesthetic drug product, it will be necessary for the sponsor to submit data to characterize local drug exposure in addition to systemic drug exposure.[9] Because of the unique product-specific characteristics of local anesthetic drug products with prolonged duration of effect, if a sponsor decides to conduct only relative bioavailability PK studies to support its local anesthetic drug product, or is considering exploring a modeling approach with available in vitro and in vivo data, the sponsor should discuss the plans with the Division early in the drug product development program.

B. Human Factors Engineering Evaluation

Sponsors should use human-factors engineering (HFE) processes throughout the development of a local anesthetic drug product. The application of HFE processes during drug product development maximizes the likelihood that the product user interface, which includes all points of interaction between the drug product and the users (e.g., delivery device, packaging labeling, including labels), allows for safe and effective use by the intended users for intended uses and

[9] As stated in section III.A., General Clinical Pharmacology Considerations, if the sponsor plans to collect PK samples for local drug exposure and characterize its PK profile, the sponsor should propose a reliable methodology or approach to accurately measure local drug concentrations and discuss the proposal with the Division early in development.

use environments. Sponsors should refer to relevant FDA guidance documents that provide information on human factors and product design.[10]

C. Trial Design

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

- The sponsor should design trials to demonstrate that the drug product is effective when used in each of the anatomical sites and surgical procedures for which an indication is sought. Alternatively, the sponsor should provide justification for the extrapolation between anatomical sites and methods of administration.

- The sponsor should select the primary outcome measure based on the proposed indication and the population being evaluated. If several validated instruments are available to assess the outcome, the choice of instrument is at the discretion of the sponsor; however, the sponsor should provide a rationale for the selection.

  — The Agency distinguishes between indications for local anesthesia and local analgesia. *Local anesthesia* is defined as the local loss of all sensation; *local analgesia* is defined as the local reduction or elimination of pain. Therefore, instruments assessing level of pain will only support an analgesic indication. Evaluation of the drug product's effects on the other sensory (e.g., temperature and pressure) and motor parameters will also be necessary in addition to the evaluation for pain sensation to adequately evaluate the safety profile of the drug product if an indication for local anesthesia is sought.

- The sponsor should evaluate the drug in a patient population that reflects the demographics of the patient population to whom the drug product will ultimately be administered.

- The sponsor should conduct blinded and randomized controlled trials to evaluate the doses, regimens, and methods of administration identified and evaluated in phases 1 and 2 of the drug product development program.

- To select the optimal dosing regimen for the indication, the Agency recommends that the sponsor conduct a dose ranging study or studies before the phase 3 clinical trial(s) or evaluate several doses in in an adequate and well-controlled phase 3 trial. Sponsors should evaluate total dose (e.g., mg), volume, and concentration of the product. In

[10] Guidances on this topic include, but are not limited to, the guidance for industry *Safety Considerations for Product Design to Minimize Medication Errors* (April 2016), the guidance for industry and FDA staff *Applying Human Factors and Usability Engineering to Medical Devices* (February 2016), the guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022), and the draft guidances for industry and FDA staff *Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications* (September 2018) and *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development* (February 2016). When final, these guidances will represent the FDA's current thinking on these topics.

addition, dose selection for local anesthetic drug product studies should take into consideration the pharmacologic properties of the drug product, target patient population, and probable concomitant medications.

- Controls should include an immediate-release or modified-release local anesthetic drug product, or both if appropriate, which are already approved for the indication under study. In addition, one of the active comparators should reflect the current standard of care. 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.

  — In certain instances, the drug product could also be compared to itself in trials designed to evaluate the efficacy of differing concentrations, doses, or dosing regimens. In such trials, a significant difference (from both statistical and clinical perspectives) in efficacy between two treatment arms could serve as evidence of efficacy for the concentration, dose, or dosing regimen that was shown to be superior to another regimen evaluated.

- Sponsors should consider current clinical practice (e.g., multimodal perioperative pain regimens) and incorporate these practices in both investigational drug and control arms, as appropriate, to obtain data, which are clinically meaningful and relevant to health care providers.

- Trials should include an adequate subject follow-up period after drug product administration and assessments at appropriate time intervals to evaluate the following:

  — Systemic and local toxicity
  — Clinical response, including clinically meaningful measures of benefit and function

D. Clinical Evaluation — Efficacy

Early in the development program, the sponsor should decide which formulation and method of delivery will be marketed. This includes, but is not limited to, the type of device design and whether it will be a generally available FDA-approved/cleared device or a device constituent part of a combination product. To support approval, the sponsor should use the final to-be-marketed product (including drug product formulation and its delivery device, if applicable) and the dosing regimen proposed for inclusion in the drug product labeling in the PK studies and clinical trials. If a product other than the final to-be-marketed product is used, the sponsor may need to conduct bridging studies or provide justification to address differences in the formulations or devices.

1. Pharmacodynamic Profile

Ideally, sponsors are able to characterize pharmacodynamics of the drug during phase 1 and phase 2 clinical trials and confirm with the findings in phase 3 trials. The sponsor should characterize the onset and duration of action of the drug product for the proposed indication. If the sponsor seeks more than one indication and the indications vary significantly in terms of the

route(s) of administration, the length of time for which anesthesia or analgesia is required, or the level of required anesthesia or analgesia (e.g., intraoperative versus postoperative anesthesia or analgesia), the sponsor should characterize the onset and duration of action of the drug product for each proposed indication. This information should be the basis for determining the time to redosing, if redosing is appropriate.

In addition, for drug products that may be used on a variety of tissue types (e.g., epidermis, dermis, muscle, perineural, bone) and/or in anatomic compartments, which differ in size and vascularity (e.g., posterior capsule of the knee versus abdominal cavity versus thoracic cavity), the evaluations should determine if those uses lead to substantial differences in the onset or duration of action of the drug product. The sponsor should include sufficient data about these differences in its NDA submission to adequately inform labeling and guide health care providers in the appropriate use of the drug product.

2. Indications

In general, the indication of a local anesthetic drug product will be limited to the type of surgical models or anatomical sites studied in the drug product development program.

a. Incisional infiltration/instillation

For a new local anesthetic drug product, if the sponsor is proposing a surgery-specific or an anatomical site-specific indication, at least two adequate and well-controlled studies will be necessary. For a modified-release formulation of a previously approved local anesthetic drug product, if the sponsor is proposing a surgery-specific or an anatomical site-specific indication, at least one adequate and well-controlled trial will be necessary. For a generalized incisional infiltration/instillation indication, at the minimum, the sponsor should establish efficacy in a bony compartment model, small and large soft tissue models, and a highly vascular compartment model (e.g., intercostal space). However, additional models may be necessary based on the drug formulation, dosing and administration, and consistency in efficacy across models demonstrated in the drug product development program.

b. Peripheral nerve block (e.g., interscalene nerve block)

There is a large variability in the types of peripheral nerve block procedures performed for surgical anesthesia and analgesia. The ability to visualize and access the target nerve, which varies with the anatomy adjacent to the target nerve (including major vessels and other tissues), will potentially impact the dose and/or volume of drug product necessary to achieve the desired degree and duration of the block. Therefore, extrapolation from one nerve block to another is difficult. Consequently, the indication will likely be limited to nerve blocks for which safety and efficacy have been demonstrated in the drug product development program.

c. Fascial plane block (e.g., transverse abdominis plane block)

The type of anatomical tissues exposed to the local anesthetic drug product in a fascial plane block (e.g., skin, subcutaneous tissues, fat, muscle) may differ significantly from incisional

infiltration/instillation (e.g., skin, subcutaneous tissues, fat only) and peripheral nerve block administration (e.g., skin, subcutaneous tissues, fat, muscle, nerve sheath, large vessels). Therefore, studies demonstrating both safety and efficacy in a fascial plane block model will be necessary to support such an indication. If efficacy and safety of the drug product has already been established for an incisional infiltration/instillation indication or peripheral nerve block indication, at least one additional trial will be necessary to be considered for a fascial plane block indication. Alternatively, the sponsor can provide an evidence-based rationale to support extrapolation from incisional infiltration/instillation or peripheral nerve block to a fascial plane block. Sponsors should consult the Division regarding extrapolation.

d. Neuraxial block (e.g., spinal or epidural block)

The development of local anesthetic drug product formulations with prolonged duration of effect for neuraxial use is challenging because of safety concerns, such as the potential for prolonged muscle weakness leading to increased risk of fall, the potential for cephalad spread leading to respiratory insufficiency or total spinal anesthesia, and spinal cord/spinal nerve toxicity because of prolonged exposure to the drug product. Therefore, sponsors should consult the Division before initiating a neuraxial block drug product development program for a local anesthetic drug product with prolonged duration of effect.

3. Fixed-Combination Drug Product

For purposes of this guidance, a fixed-combination drug product (FCDP) is one in which two or more active ingredients are combined at a fixed dosage in a single dosage form. When developing an FCDP, the sponsor must demonstrate that each active ingredient makes a contribution to the claimed effect of the combination drug product, as defined in 21 CFR 300.50. The demonstration of such contribution may require a properly designed factorial trial. In addition, the benefit of the proposed combination of active ingredients must outweigh any additional risk posed by the combination.[11, 12]

4. Combination Product

If developing a combination product, the design of the product user interface should be assessed in human factors studies, as appropriate, to demonstrate that the proposed combination product user interface allows for safe and effective use in addition to addressing human factors considerations (see section III.B., Human Factors Engineering Evaluation). The application should address the safety and effectiveness of the to-be-marketed combination product including the device constituent part. Also, combination products are subject to 21 CFR part 4 subpart A, Current Good Manufacturing Practice Requirements for Combination Products.[13] The type of data to submit for the device constituent part is beyond the scope of this guidance. Developers of

[11] For additional information, see the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination* (June 2013).

[12] See 21 CFR 300.50.

[13] See the guidance for industry and FDA staff *Current Good Manufacturing Practice Requirements for Combination Products* (January 2017).

local anesthetic combination products with prolonged duration of effect should request early development discussions with the Division.

5. Efficacy Endpoints and Analyses

The recommended primary efficacy endpoint for the evaluation of the postoperative analgesic effect of a local anesthetic drug product is the AUC of pain scores. The clinical pain scale(s) utilized to assess pain should be validated in the patient population(s) being studied. The schedule of assessments should be appropriate to evaluate the clinical endpoints and reflect the PK and PD profiles of the proposed local anesthetic drug product. Because the PK and PD profile may vary with each drug product, it is necessary to demonstrate superiority or noninferiority relative to the comparator during the entire proposed duration of effect, most importantly the later time points.

Efficacy analyses should include the following:

- Comparison of primary endpoint(s) using the appropriate statistical methods.

- Consideration of adjustment for prognostic covariates (e.g., baseline pain) to potentially improve precision of treatment effect estimate and study power if linear model assumption holds.

- Prespecification of estimand of interest, including strategy for handling rescue medication use.

- Planned sensitivity analyses to evaluate sensitivity to violations in missing data assumptions.

- Presentation of mean pain scores over the entire treatment period. These pain curves should demonstrate continuous benefit or similarity of the local anesthetic drug product relative to the comparator during a clinically meaningful trial period.

  — In general, comparison of the changes in the mean pain scores of treatment groups at a single time point is not an appropriate analysis of efficacy because such comparison may be difficult to interpret from a clinical perspective. Therefore, the sponsor should evaluate a range of time points, specifically focusing on later time points, that can demonstrate an extended efficacy profile (e.g., 48 to 72 hours). The sponsor can evaluate additional later time points, as appropriate.

  — The AUC approach is a weighted average across the specified time frame. Weights are determined by the length of time between each observed pain score. Benefits include the ability to vary the timing of planned observations (e.g., short intervals early in treatment to capture time to the onset of action) and to account for use of rescue medication by recording unscheduled pain scores before administration of rescue medication.

— Presentation of pain scores over time can:

- Include the point estimate and the 95 percent confidence interval of the mean pain scores at each postsurgical time point when the pain curve over the entire postsurgical treatment period is presented.

- Present pain score over the entire postsurgical time period by trial subject for the intent-to-treat subjects in one pain score graph.

At a particular time point, some trial subjects may fare well while others fare poorly in the same treatment group, and yet, the mean group response may be favorable. One approach is to compare the number of subjects reaching prespecified criteria for success, i.e., a responder analysis. It is important that a responder analysis incorporate a criterion of improvement in the primary endpoints along with criteria for use of rescue medication and other outcome measures. FDA encourages sponsors to explore a variety of outcome measures and responder definitions during phase 2 trials to provide a rationale for use of a responder analysis as the primary analysis in phase 3 trials.

Sponsors should contact the Division for recommendations on the adequacy of the trial endpoints and additional analyses for specific local anesthetic drug product development programs.

If a sponsor decides to pursue both surgical anesthesia and postoperative analgesia indications, the sponsor should discuss such plans with the Division early in the drug product development process.

E. Clinical Evaluation — Safety

The sponsor should address the following safety aspects, as appropriate, for the proposed local anesthetic drug product with a prolonged duration of effect:

- All established safety risks associated with the immediate-release local anesthetic drug product that is being developed into a modified-release formulation and the potential general safety implications of extending its duration of action.

- The safety of any novel inactive ingredients in the drug product formulation or novel device or device constituent parts.

- Risks of local exposure at the site of administration (e.g., infection, wound dehiscence, nerve toxicity).

- Risks of systemic exposure (i.e., local anesthetic systemic toxicity assessments).

- Risks of prolonged or permanent neurologic deficits, or any outcomes of unresolved/ongoing sensory or motor deficits (e.g., falls, inability to undergo physical rehabilitation). Full recovery of both sensory and/or motor function must be demonstrated.

- Safety of repeated dosing, including time frame and dose adjustments, if necessary.

- Safety and compatibility of concomitant drugs (e.g., coadministration with immediate-release local anesthetic drug products, anesthetic adjuncts such as epinephrine).

IV. CONSIDERATIONS FOR LABELING CLAIMS

A. Superiority Claims

For a claim of superiority in the prescribing information, the sponsor needs to demonstrate that the proposed local anesthetic drug product is superior to an approved drug product from both statistical and clinical perspectives using clinically relevant efficacy or safety endpoints in replicated adequate and well-controlled trials making direct comparison to the approved drug product for each proposed indication.[14] In addition, to claim superiority, the sponsor must establish a positive benefit-risk profile of the proposed product compared to the approved drug product.

B. Novel Endpoints

There is great public health interest in assessing additional, clinically meaningful endpoints such as reduction in hospitalization or rehospitalization, emergency department visits, or death caused by opioid abuse, as well as improvements in the ability to resume work, school, or other productive activities. FDA recognizes that evaluating these outcomes could require larger trials than those usually conducted for marketing approval. However, collecting data on clinically meaningful outcomes would be highly valuable, and FDA encourages sponsors to consider collecting such data even if not intended to support a regulatory decision. Furthermore, using these outcomes as clinical trial endpoints could provide the basis for inclusion in the FDA-approved labeling.

Sponsors should support novel endpoints with data demonstrating that the endpoints represent a clinically meaningful benefit. Additional research may be necessary to develop or better define instruments to measure these patient-reported outcomes[15] or other novel endpoints in clinical trials (e.g., improvement in rehabilitation or recovery). For endpoints related to the reduction in opioid analgesic drug products use, *opioid-sparing* claims, and data needed to support such claims, sponsors should refer to the draft guidance for industry *Development of Non-Opioid Analgesics for Acute Pain* (February 2022).[16]

[14] For additional information, see the guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2006).

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

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

If a sponsor plans to include novel endpoints in a local anesthetic drug product development program, FDA strongly encourages the sponsor to discuss such plans with the Division early in the drug product development process.