

NDA 214044

NDA APPROVAL

Athena Bioscience, LLC
c/o Sovereign Pharmaceuticals, LLC
7590 Sand Street
Fort Worth, TX 76118

Attention: Ruth Collins, RAC
Manager, Regulatory Affairs

Dear Ms. Collins:

Please refer to your new drug application (NDA) dated and received November 1, 2019, received, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for QDOLO (tramadol hydrochloride) oral solution, 5 mg/mL.

This new drug application provides for the use of QDOLO in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) as well as annual reportable changes

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CONTAINER LABEL

Submit the final printed container label that is identical to the enclosed container label submitted on August 13, 2020, as soon as it is available, but no more than 30 days after it is printed. Please submit the labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 214044.**” Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

The dating period for QDOLO shall be 24 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F). [see USP Controlled Room Temperature].

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for the pediatric age group less than 12 years of age because a pediatric assessment including clinical studies of tramadol hydrochloride would be unsafe in this population based on the contraindication to its use in this age group.

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

We are also deferring submission of your pediatric assessment for ages 12 to less than 17 because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study(ies) required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act/FDCA are required postmarketing studies. The status of these postmarketing study(ies) must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act/FDCA. These required studies are listed below.

- 3918-1 Conduct a juvenile animal toxicology study to characterize the impact of tramadol on brain development, to support pediatric dosing in adolescent patients 12 to less than 17 years of age.

Draft Protocol Submission:	09/2020
Final Protocol Submission:	11/2020
Study Completion:	05/2022
Final Report Submission:	03/2023

- 3918-2 Conduct a randomized, double-blind, placebo-controlled study evaluating the clinical effectiveness, safety, and pharmacokinetic profiles of QDOLO (tramadol hydrochloride) oral solution in pediatric patients 12 to less than 17 years of age, outside of the contraindicated setting of tonsillectomy and/or adenoidectomy.

Draft Protocol Submission:	Complete
Final Protocol Submission:	12/2020
Study Completion:	02/2024
Final Report Submission:	08/2024

FDA considers the term final to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.³

Submit the protocol(s) to your IND 127021, with a cross-reference letter to this NDA. Reports of this/these required pediatric postmarketing study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this/these study(ies). When submitting the reports, please clearly mark your submission "SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS" in large font, bolded type at the beginning of the cover letter of the submission.

³ See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019)*.
<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for QDOLO (tramadol hydrochloride) oral solution to ensure the benefits of the drug outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse.

Your proposed REMS must also include the following:

Medication Guide: In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that QDOLO poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of QDOLO. FDA has determined that QDOLO is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use QDOLO. Under section 505-1 of the FDCA, FDA has also determined that a Medication Guide is necessary to ensure the benefits of the drug outweigh the risks (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed QDOLO.

Elements to assure safe use: Pursuant to 505-1(f)(1), we have also determined that QDOLO can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse that are listed in the labeling.

Your REMS includes the following elements to mitigate these risks:

- Healthcare providers have particular experience or training, or are specially certified

This REMS uses a shared system for the elements to assure safe use and the REMS assessments. This shared system, known as the Opioid Analgesic REMS program, includes the products listed on the FDA REMS website available at <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>.

The proposed REMS, submitted to Drug Master File (DMF) (b) (4), amended and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce ODOLO (tramadol hydrochloride) into interstate commerce. Because QDOLO will be a member of the Opioid Analgesic REMS (approved September 18, 2020), the assessment plan will be the same assessment plan required for the other products covered by this shared system REMS. Because the 6- month and 12-month assessment reports for the Opioid Analgesic REMS have already been submitted, and the 24-month report will not include this product, the first assessment report that includes QDOLO will be due September 18, 2021. This reporting date will align with the 36-month report for the Opioid Analgesic REMS.

Submission of subsequent REMS assessment reports for QDOLO will align with the assessment reports of the Opioid Analgesic REMS.

Therefore, your REMS assessment plan must include, but is not limited to the following:

1. REMS Outreach and Communication

- a. For each healthcare provider (e.g., prescriber, pharmacist) to be sent information regarding REMS-compliant accredited continuing education (CE), provide the date when the letters were sent; the number of letters electronically sent, received, undeliverable, and opened; and the number of letters mailed and undeliverable.
- b. For each professional society, association, and licensing board to be sent information regarding REMS-compliant accredited CE, provide the number of letters electronically sent, received, undeliverable, and opened; and the number of letters mailed and undeliverable.

2. REMS Implementation and Operations

- a. Status of grants
 - i. The status of the request for proposals for grants for REMS-compliant accredited CE including:
 1. Request for Application (RFA) issued: date and number of applications submitted in response to each RFA
 2. RFAs awarded: date, number, and name of grantee
 3. Date/timeframe next RFA to be issued

- ii. The status of the requests for proposals for any grants to CE Providers or other CE organizations with expertise in assessing CE outcomes who agree to conduct evaluations of health care providers who have taken REMS-compliant accredited CE funded under this REMS.
- b. Grant review committee
- i. Individuals from the REMS Program Companies (RPC) reviewing grants will include the following clinical licensures: pharmacists, nurses, physicians. Additionally, there will be involvement by individuals with regulatory and pharmacovigilance experience. The job title, licensure, and professional degree of individuals will be provided for each grant review cycle.
 - ii. Include any external members (non-RPC) involved in the grant review, including those from the broad-based CE community. Provide the job title, licensure and professional degree of the individual for each grant review cycle
- c. For CE programs awarded during the assessment period:
- i. Description of each grantee and projected number of completers
 - ii. For the first assessment, the date the first program based upon the FDA Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain (“FDA Blueprint”), became available
 - iii. Description of CE program:
 - 1. Level of outcome the activity⁴ is designed to impact
 - 2. CE format (live, webinar, etc.)
 - 3. Duration of activity for live or webinar activities
 - 4. Average duration to complete for internet/enduring activities
 - 5. Education methods and tools (case-based, multimedia, didactic, interactive, adaptive, etc.)^{5,6}
 - iv. All reports submitted to the RPC by CE grantees during the assessment period.

⁴ Stevenson R, Moore DE. Ascent to the Summit of the CME Pyramid. JAMA 2018;319(6):543-544.

⁵ Cervero R, Gaines J. The Impact of CME on Physician Performance and Patient Health Outcomes: An Updated Synthesis of Systematic Reviews J Contin Educ Health Prof 2015;35(2):131–138.

⁶ Agency for Research Health and Quality. (2007). Effectiveness of Continuing Medical Education. Retrieved May 9, 2018, from <https://archive.ahrq.gov/downloads/pub/evidence/pdf/cme/cme.pdf>.

- d. Number of completers of OA REMS Continuing Education activities during the assessment period; provide description of learners by standard learner category data.⁷
 - i. Summary of reports from any CE Provider that tracks participants that begin an activity but do not complete it; only provide when insight on lack of completion is available (e.g., participant didn't complete because activity too long, too difficult, etc.)
- e. Independent Audit: The results of independent audits of the CE. Audits must be conducted on a random sample of at least 10% of the REMS-compliant accredited CE funded under the Opioid Analgesic REMS and must include/evaluate:
 - i. a description of the organization(s) conducting the audit(s)
 - ii. whether the content of the REMS-compliant accredited CE covers all elements of the FDA Blueprint approved as part of the REMS;
 - iii. whether the integrated or post-course knowledge assessment measures knowledge of all sections of the FDA Blueprint; and
 - iv. whether the REMS-compliant accredited CE was conducted in accordance with the Accreditation Council for Continuing Medication Education (ACCME) standards for CE or appropriate standards for accreditation bodies
- f. Concurrent Educational Interventions
 - i. For the year prior to the assessment period through the assessment period, provide an evaluation of the overall pain/opioid CE landscape including but not limited to:
 - 1. States requiring prescribers, pharmacists or nurses to complete opioid or pain management continuing education for licensing/renewal of licensing:
 - a. enumeration of these states and their requirements for continuing education on either pain or safe opioid use,
 - b. estimates of annual licensed prescribers in those states
 - c. which, if any, opioid analgesic or Extended-Release/Long-Acting ("ER/LA") Opioid Analgesic

⁷ Standard Continuing Education (CE) learner data to be captured by all CE Providers for Opioid Analgesic REMS includes geographic location (state of primary practice), DEA prescriber status (individual registration or institutional authorization), profession, practice area, and length of time in practice.

REMS CE (i.e., current and former REMS program) were permissible in which states, for prescribers to meet requirements

2. Health systems, including government (DOD, VA, IHS, etc.), that require opioid or pain management continuing education; include number of completers if available
 3. Any additional available data on continuing education programs available during this time with a focus on pharmacological pain management or safe opioid use
3. Health Outcomes and/or Surrogates of Health Outcomes
- a. Surveillance and monitoring of data relating to opioid analgesic use, misuse, abuse, overdose, addiction, and death. Surveillance data should include the following:
 - i. Nationally representative data or data from large stable populations on opioid analgesic misuse, abuse, addiction, overdose, and death, to allow reliable assessment of national trends and demographic patterns (e.g., age group specific rates and trends)
 - ii. Both overall and drug-specific outcome rates, as available, in each data source
 - iii. Data on trends and patterns of illicit opioid (e.g., heroin) use and related morbidity and mortality
 - b. Evaluation of drug utilization patterns: Nationally-projected data on drug utilization trends and patterns, including an evaluation of trends in:
 - i. Dispensing of opioid analgesics subject to the Opioid Analgesic REMS, by drug, age group, prescriber specialty
 - ii. An evaluation of opioid tolerance for products that require patients to be opioid tolerant prior to use
 - iii. Patient-level evaluation of concomitant prescribing of gabapentinoids, benzodiazepines, and other CNS depressants with opioid analgesics
 - c. An evaluation of patients' experiences with acute and chronic pain management in various settings: this may include a survey, focus group, or other assessment of patient experience, including but not limited to access to coordinated pain management care, non-pharmacological options, and judicious and informed prescribing of opioids. The evaluation may also include an assessment of negative patient experiences, such as perceived overprescribing of opioids, providers' refusal to provide care, or forced rapid tapering or discontinuation.

- d. Evaluation of prescriber behavior and patient outcomes: The results of an evaluation of the effect of REMS-compliant CE on prescriber behavior and patient outcomes. This evaluation should include the following:
 - i. Development and use of metrics that assess prescriber behaviors and patient outcomes relating to key messages in the FDA Blueprint. The assessment should also include an evaluation of potential unintended adverse patient outcomes resulting from changes in prescribing practices (e.g., withdrawal symptoms or increased pain due to inappropriate rapid opioid tapering, patient abandonment, seeking of illicit opioids, suicide attempts/completion)
 - ii. Use of an appropriate control group (i.e., providers who have not completed REMS-compliant accredited CE), and rigorous control for confounding, to allow an assessment of whether any observed changes in prescriber behaviors or patient outcomes can be attributed to the CE
- e. Evaluation of healthcare providers' perceptions of the key influences (e.g., education, state legislation, system-level policies, fear of reprimand or litigation, insurance reimbursement, time constraints) on pain management practices for prescribers and other members of the healthcare team and what the impacts have been on patient outcomes. For the 24-month assessment,
 - i. Conduct a literature review and summarize previous work in this area.
 - ii. Propose a study or studies to address the evaluation of the key influences on a sample of opioid prescribers. These studies may employ mixed-methods approaches and other emerging research methodologies most appropriate for answering the question.

4. Knowledge

- a. Evaluation of CE participants: The results of evaluations to determine the impact of REMS-compliant accredited CE on participants' knowledge, attitudes, and self-reported behavior around pain management and appropriate opioid prescribing. All evaluations should be representative and generalizable to the targeted health care professionals taking the REMS-compliant accredited CE and assess understanding of key elements from all sections of the FDA Blueprint. Multiple methodologies should be used, including but not limited to the following:
 - i. These assessments could be integrated into live, online, or multimedia formats using interactive approaches to enhance the educational value of the activity. Different versions or subsets of

- questions from a standardized assessment tool could be employed to cover all key messages and sections of FDA Blueprint, in aggregate, while reducing the time burden for individual participants and allowing the assessment to be tailored for different types of healthcare professionals.
- ii. A long-term follow-up evaluation of participants to assess retention of knowledge and skills, application of learning to clinical practice, self-reported change in behavior, and barriers to change. Consider incentivizing participation in follow-up assessment, for example through additional CE credits.
 - b. Evaluation of Patient Understanding: The results of an evaluation of patients' and caregivers' understanding of the serious risks of opioid analgesics and their understanding of how to use these products safely. This evaluation may include, for example, surveys of patients from a representative sample of patients taking opioid analgesics with respect to education level, insurance status, and geographic location.
5. During transition from the ER/LA Opioid Analgesics REMS to Opioid Analgesic REMS, data to be included until the last enduring activity has been reported:
 - a. For each CE activity released under the ER/LA Opioid Analgesics REMS that remains active, provide the name of the CE Provider, the title of the activity, and the date the activity will expire
 - b. Aggregate data on participants and completers should be collected using original MEMS 2.0 definitions
 6. Methodologies: A timeline for submission of the assessment protocols, including data sources and the methodologies used to conduct all the above described analyses. Each assessment report should update the dates of submission for each component of the assessment.
 7. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) *If the new, proposed indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification, provide a rationale for why the REMS does not need to be modified.*

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 214044 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g.,

**ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES,
AUDIT PLAN, DRUG USE STUDY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 214044 REMS ASSESSMENT

or

**NEW SUPPLEMENT FOR NDA 214044/S-000/
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 214044/S-000/
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 214044/S-000/
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX**

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 214044/S-000/
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 214044

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.⁸

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.⁹ Information and Instructions for completing the form can be found at FDA.gov.¹⁰

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

⁸ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

⁹ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

¹⁰ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

If you have any questions, call Matthew Sullivan, MS, RAC, Chief of Project Management Staff, at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Naomi Lowy, MD
Deputy Director (Acting)
Division of Anesthesiology, Addiction Medicine
and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
 - Prescribing Information
 - Medication Guide
- Container Label
- REMS

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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