NDA 207932/S-027

SUPPLEMENT APPROVAL

BioDelivery Sciences International, Inc.
c/o Collegium Pharmaceutical
100 Technology Center Drive, Suite 300
Stoughton, MA 02072

Attention: Heta Mehta
Senior Manager, Regulatory Affairs

Dear Heta Mehta:

Please refer to your supplemental new drug application (sNDA) dated and received February 5, 2024, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Belbuca (buprenorphine buccal film).

This Prior Approval sNDA provides for a proposed modification to the approved opioid analgesic risk evaluation and mitigation strategy (OA REMS). This supplement is in response to our April 3, 2023, REMS Modification Notification letter.

We have completed our review of this application. It is approved, effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The Shared System (SS) REMS for opioid analgesic products intended for use in the outpatient setting (OA REMS), of which Belbuca is a member, was originally approved on July 9, 2012, and the most recent REMS modification was approved on November 14, 2019. The SS REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS.

In order to ensure the benefits of Belbuca outweigh its risks, we determined that you were required to make the REMS modifications outlined in our REMS Modification Notification letter dated April 3, 2023. Specifically, a safe disposal system in the form of mail-back envelopes that are made available for dispensing to certain patients, is necessary as it may mitigate the serious risks of overdose and abuse. In addition, the following modifications were communicated during the course of the review:

- The REMS goal was modified to the following:

The goal of the Opioid Analgesic REMS is to mitigate the risks of addiction, abuse, and misuse, which can lead to overdose and death. The Opioid Analgesic REMS is

one of many national, state, and local efforts to address the misuse and abuse of prescription opioid analgesics (OA).

The REMS will be assessed through these objectives:

- Objective 1: Healthcare providers involved in the treatment and monitoring of patients in pain (including pharmacists and nurses) are educated on recommended pain management practices, including counseling patients and appropriate OA prescribing
- Objective 2: Patients are educated on the risks of OAs and the need for proper storage and disposal of OAs
- Objective 3: Patients are offered a safe disposal system as an option to safely dispose of unused OAs

- Addition of a process for pharmacies and other dispensers to order the mail-back envelopes via online or by phone.

Your proposed modified REMS, submitted to Drug Master File (DMF) 031551 on January 29, 2024, amended and appended to this letter, is approved. The modified REMS consists of elements to assure safe use, Medication Guide, a disposal requirement, and a timetable for submission of assessments of the REMS.

This shared system REMS, known as the OA REMS, currently includes products listed on the FDA REMS website[1].

Other products may be added in the future if additional NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS must be revised to submit assessment reports on September 18, 2025, June 1, 2026, September 18, 2026, and annually thereafter (from September 18, 2026).

The revised REMS assessment plan must include, but is not limited to, the following:

1. REMS Outreach and Communication (Beginning with the September 2025 Assessment Report and annually thereafter)

    a. For each health care provider (HCP) (e.g., prescriber, pharmacist) sent information regarding REMS-compliant accredited continuing education (CE) and the REMS-provided safe disposal option (e.g., pre-paid drug mail-back envelopes (MBEs)), 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.

[1] https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

b. For each professional society, association, and licensing board sent information regarding REMS-compliant accredited CE and the REMS provided safe disposal option (e.g., pre-paid drug MBEs), provide the number of letters electronically sent, received, undeliverable, and opened; and the number of letters mailed and undeliverable.

2. REMS Implementation and Operations (Beginning with the September 2025 Assessment Report and annually thereafter)

   a. Safe disposal system (i.e., pre-paid drug MBEs)

      Analyze data at the level of individual pharmacy locations and other locations of dispensers of opioid analgesics intended for outpatient use, instead of at the district, regional, or corporate level.

      i. The number of individual pharmacies and other dispensers of opioid analgesics intended for outpatient use that ordered pre-paid drug MBEs, including the number of times each ordered and quantity of pre-paid drug MBEs each ordered.

      ii. The total number of pre-paid drug MBEs ordered by all pharmacies and other dispensers of opioid analgesics intended for outpatient use.

      iii. The total number of pre-paid drug MBEs ordered by all pharmacies and other dispensers of opioid analgesics intended for outpatient use that were received and/or destroyed at the destruction site.

      iv. The total number of destroyed pre-paid drug MBEs per originating ordering site.

      v. Annual pharmacy surveys about use of pre-paid drug MBEs and other disposal options. Surveyed population should include dispensing locations that ordered pre-paid drug MBEs and dispensing locations that did not order pre-paid drug MBEs.

      vi. Pre-paid drug MBE order form metrics

         1. Number of pharmacies that reordered pre-paid drug MBEs at least once.

         2. Median, mean, range of pre-paid drug MBE orders/quantity per pharmacy.

         3. Summary characteristics of pharmacies that ordered pre-paid drug MBE, including but not limited to: geographical

distribution, pharmacy type (chain, independent, specialty, hospital outpatient, hospice, assisted living, nursing home).

4. For pharmacies that reorder pre-paid drug MBEs, summary information about how pharmacies distributed pre-paid drug MBEs.

5. Summary information about whether pharmacies that order pre-paid drug MBEs also offer other opioid analgesics (OA) disposal options.

b. 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 for 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 HCPs who have taken REMS-compliant accredited CE funded under this REMS.

c. Grant review committees (GRC)

   i. Individuals from the REMS Program Companies (RPC) reviewing grants as part of the GRC may include the following clinical professionals: pharmacists, nurses, physicians. Additionally, there will be involvement by individuals with regulatory and pharmacovigilance experience. Provide the job title, licensure, and professional degree of the individuals for each grant review cycle.

   ii. Include any external members (non-RPC/Independent Grant Review Committee (IGRC)) involved in the grant review, including those from the broad-based CE community. Provide the job title, licensure and professional degree of the individuals for each grant review cycle.

d. For CE programs awarded during the assessment period:

   i. Description of each grantee and projected number of completers.

   ii. Description of CE program:

1. Level of outcome the activity is designed to impact
2. CE format (live, webinar, etc.)
3. Number of credit hours by format of activity
4. Education methods and tools (case-based, multimedia, didactic, interactive, adaptive, etc.)

iii. All reports submitted to the RPC by CE grantees during the assessment period.

e. Number of completers of OA REMS Continuing Education (CE) activities during the assessment period. Provide description of learners by standard learner category data.

i. Table and a graphical representation of CE completers by year and cumulatively from the inception of the Extended-Release/Long Acting (ER/LA) Opioid Analgesic REMS on July 9, 2012 through the current reporting period based on the formal data collection process obtained through the CE accreditors. Note the date of first available OA REMS CE activity and date of last ER/LA REMS activity counted.

f. 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* [2] approved as part of the REMS.

iii. Whether the integrated or post-course knowledge assessment measures knowledge of all sections of the *FDA Blueprint* [2].

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.

3. Health Outcomes and/or Surrogates of Health Outcomes

[2] Refer to the *FDA Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain* (October 2023) at https://www.fda.gov/media/173774/download.

a. Surveillance and monitoring of data relating to opioid analgesic use, misuse, abuse, overdose, addiction, and death (reported every two years, beginning with the September 2026 Assessment Report). 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. This evaluation should include trends, reported in calendar year time-periods, according to the timing indicated below:

    i. Dispensing of opioid analgesics subject to the Opioid Analgesic REMS, by drug, age group, prescriber specialty (reported every year, beginning with the September 2025 Assessment Report).

    ii. A patient-level evaluation of concomitant prescribing of gabapentinoids, benzodiazepines, and other Central Nervous System (CNS) depressants with opioid analgesics (reported every year, beginning with the September 2025 Assessment Report).

    iii. Provide an assessment of the number of opioid providers in the United States (the Prescriber Volume Study) (reported every two years, beginning with the September 2025 Assessment Report).

c. Surveillance and monitoring over time of self-reported opioid analgesic storage and disposal practices and attitudes, among people using prescribed opioid analgesics in the past year, in one or more nationally representative general U.S. population surveys. (Beginning with the September 2025 Assessment Report and annually thereafter)

    i. Reporting periods

        1. Pre-implementation of pre-paid drug MBEs:

            a. Begin collecting these data for approximately the year before implementation of pre-paid drug MBEs (e.g.,

data captured in the first quarter (Q1) of 2025 to cover participants' experience prior to implementation of pre-paid drug MBEs).

b. Use this information as a comparison period in annual REMS assessment reports, thereafter.

2. Post-implementation of pre-paid drug MBEs:

a. Report these data according to the reporting period for the annual REMS assessment reports.

b. The reporting period for these data must include Q1 of the same year as the REMS assessment report.

c. For any reporting period for which the prior year includes time both before and after implementation of pre-paid drug MBEs, disaggregate the pre- and post-periods, to the extent possible. For example, report Q1 and Q3 surveys separately, if applicable.

ii. Reporting metrics

1. Among people with opioid analgesic prescriptions in the past year:

a. Number and proportion of people who were offered different disposal options or education with their opioid analgesic prescription (to include at a minimum: pre-paid drug MBEs, in-home disposal systems, flushing, disposal kiosk, take-back programs, disposing in the trash, no disposal option, education; with multiple selections allowed) in the past year.

b. Number and proportion of people who used different storage options for opioid analgesics (to include at a minimum: medicine cabinet, lock box, pill case; with multiple selections allowed) in the past year.

c. Number and proportion of people with unused opioid analgesics at the end of a course of treatment in the past year.

2. Among people prescribed an opioid analgesic in the past year with unused opioid analgesics at the end of a course of treatment:

a. Number and proportion of people who used different disposal options for opioid analgesics (to include at a minimum: pre-paid drug MBEs, in-home disposal systems, flushing, disposal kiosk, take-back programs, disposing in the trash, not disposing; with multiple selections allowed) in the past year.

b. Reasons for use or non-use of different disposal options for opioid analgesics (to include at a minimum: no longer need leftover opioid analgesics, child or other family in the home, concerns about others using leftover opioid analgesics, unaware of options, unable to access options such as mailboxes for pre-paid MBE return, convenience, cost, environmental concerns, kept leftover opioid analgesics for later use, concern they may not be able to obtain a new opioid analgesic prescription if future need arises; with multiple selections allowed) in the past year.

4. Knowledge (conducted annually, report beginning with the September 2025 Assessment Report and annually thereafter)

    a. HCP Survey: The results of a knowledge evaluation of HCPs who participate in the treatment and monitoring of patients who receive opioid analgesics, including prescribers, pharmacists, and nurses. The survey should evaluate knowledge of recommended pain management practices, including counseling patients, appropriate prescribing, and prescribing behavior.

    b. Patient Survey:

        i. The results of an evaluation of a representative sample of patients' and caregivers' understanding of the serious risks of opioid analgesics and their understanding of how to use, store, and dispose of these products safely, as well as use of pre-paid drug MBE and other disposal options (conducted annually). Report revised survey results with the September 2025 Assessment Report and annually thereafter.

5. Methodologies: A timeline for submission of the assessment protocols, including data sources and the methodologies used to conduct all the analyses described above. Each assessment report should include updated submission dates for each component of the assessment. (Beginning with the September 2025 Assessment Report and annually thereafter)

6. June 1, 2026, Assessment Report (Reporting Period: January 1, 2025 – December 31, 2025)

    a. On June 1, 2026, submit a one-time Assessment Report regarding pre-paid drug MBE implementation and opioid disposal for the period of January 1, 2025 – December 31, 2025. The report should include the following metrics only:

        i. Safe disposal system metrics (2.a.i, 2.a.ii, 2.a.iii, 2.a.iv, and 2.a.vi.1-5) containing data from January 1, 2025 – December 31, 2025

        ii. Health Outcomes and/or Surrogates of Health Outcomes metric 3.c (Surveillance and monitoring over time of self-reported opioid analgesic storage and disposal practices and attitudes, among people using prescribed opioid analgesics), for the period January 1, 2025 – December 31, 2025

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 one 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) of the FDCA. 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 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 that 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 REMS modifications*, provide a rationale for why the REMS does not need to be modified.

Additionally, we recommend that you submit your proposed protocols for surveillance and monitoring over time of self-reported opioid analgesic storage and disposal practices and attitudes, among people using prescribed opioid analgesics in the past year, for FDA review within 30 days of the date of this letter. Prominently identify submissions containing the assessment instruments and methodology with the following wording in bold capital letters, at the top of your cover letter and at the top of the first page of the main submission document:

> **DMF 031551 REMS ASSESSMENT METHODOLOGY / REQUEST FOR REMS ASSESSMENT METHODOLOGY PROTOCOL REVIEW** (insert concise description of content in bold capital letters, e.g., **SURVEILLANCE AND MONITORING OVER TIME OF SELF-REPORTED OPIOID ANALGESIC STORAGE AND DISPOSAL PRACTICES**).

We recommend that you submit your proposed protocols for the pharmacy surveys about mail-back envelopes and opioid disposal, healthcare provider knowledge surveys, and patient knowledge surveys for FDA review within 60 days of the date of this letter. Prominently identify submissions containing the assessment instruments and methodology with the following wording in bold capital letters, at the top of your cover letter and at the top of the first page of the main submission document:

> **DMF 031551 REMS ASSESSMENT METHODOLOGY / REQUEST FOR REMS ASSESSMENT METHODOLOGY PROTOCOL REVIEW** (insert concise description of content in bold capital letters, e.g., **PHARMACY SURVEYS, HEALTHCARE PROVIDER KNOWLEDGE SURVEYS, PATIENT KNOWLEDGE SURVEYS**)

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:

> **DMF 031551 REQUEST FOR REMS ASSESSMENT METHODOLOGY PROTOCOL REVIEW** (insert concise description of content in bold capital letters, e.g., **ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES,, 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 207932 REMS ASSESSMENT**
>
> ***or***
>
> **NEW SUPPLEMENT FOR NDA 207932/S-000**
> **CHANGES BEING EFFECTED IN 30 DAYS**
> **PROPOSED MINOR REMS MODIFICATION**
>
> ***or***
>
> **NEW SUPPLEMENT FOR NDA 207932/S-000**
> **PRIOR APPROVAL SUPPLEMENT**
> **PROPOSED MAJOR REMS MODIFICATION**
>
> ***or***

NEW SUPPLEMENT FOR NDA 207932/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 207932/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 207932

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

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling.*

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

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR

314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

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

If you have any questions, email Sandrine Ly, PharmD; Safety Regulatory Project Manager, at Sandrine.Ly@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

CDR Mark A. Liberatore, PharmD, RAC
Deputy Director for Safety
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE:
- 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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