DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022266 **NDA APPROVAL**

BioDelivery Sciences International, Inc.
801 Corporate Center Drive
Suite 210
Raleigh, NC 27607

Attention: David T. Wright, PhD, RAC
Director, Regulatory Affairs

Dear Dr. Wright:

Please refer to your New Drug Application (NDA) dated October 31, 2007, received October 31, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Onsolis (fentanyl buccal soluble film) 200, 400, 600, 800, and 1200 mcg.

We acknowledge receipt of your amendments dated November 19 and 21, 2007, and January 24, February 22 and 28, March 11 and 25, April 1, 3 (2), 16, and 21, May 7 and 9, June 9, 12, 25, and 26, July 8, August 5 (2), 19, and 22, and December 12, 2008, and February 27, March 3, 16, 23 and 31, April 14 and 24, May 15 and 22, June 12 and 26, and July 14, 2009.

The December 12, 2008, submission constituted a complete response to our August 25, 2008, action letter.

This new drug application provides for the use of Onsolis (fentanyl buccal soluble film) for the management of breakthrough pain in cancer patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert and Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 022266**."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022266."** Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages birth to less than 3 years because necessary studies would be impossible or highly impracticable to undertake. This is because the number of pediatric patients less than 3 years of age with chronic pain due to cancer and breakthrough pain is extremely small.

We are deferring submission of your pediatric study for ages 3-17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

1. Deferred pediatric study under PREA, including pharmacokinetics, efficacy and safety, for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent pain in pediatric patients ages 3-17 years old.

Final Protocol Submission Date:	January 2011
Study Completion Date:	December 2013
Final Report Submission:	May 2014

Submit the clinical protocol to your IND, with a cross reference letter to this NDA. Submit final study reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated "**Required Pediatric Assessment**".

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 (section 505-1(a)).

Your proposed REMS, submitted on July 14, 2009, and appended to this letter (with the minor editorial changes discussed with you on July 15, 2009, and incorporated in the attached version), is approved. We remind you of your agreement to update all relevant materials with the language and format of the final REMS document appended to this letter. The REMS consists of a Medication Guide, a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

1. Data (during the reporting period and cumulative) from the prescriber and pharmacy education and enrollment report from the FOCUS Program database including at a minimum:

    a. The number of prescribers enrolled in the FOCUS Program and the number of completed Prescriber Knowledge Assessments

    b. The number of patients enrolled in the FOCUS Program and the number of completed counseling call events

    c. ONSOLIS Month-to-Date Sales (Distribution) Report

    d. Dispensing activity which provides shipment confirmation and authorization to dispense data from enrolled FOCUS pharmacies

2. Results of any prescriber, pharmacy, wholesaler, and vendor audits conducted and corrective actions taken during the reporting period

3. Results of any surveys conducted of prescribers understanding and knowledge of their of the critical elements of the prescriber education for the FOCUS Program

4. Results of any surveys conducted of patients understanding and knowledge of the serious risks of Onsolis

5. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24

6. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

7. Results of surveillance and monitoring activities for abuse, misuse, and overdose including:

    a. Signals that indicate misuse, abuse, overdose, or addiction

    b. Signals that indicate serious adverse events or deaths related to inappropriate prescribing or other prescriber misuse of Onsolis, such as patients obtaining prescriptions from multiple prescribers, prescriptions to non-opioid tolerant patients, and prescriptions for inappropriate doses.

8. Drug Utilization Data including the following information:

    a. Data from flagged prescriptions from more than 2 prescribers to the same patient

    b. Any cases of prescribing and dispensing to non-opioid tolerant patients

    c. Extent of shipment delays where the patient received drug >5 business days after the original prescription was received by the pharmacy

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

The requirements for assessments of an approved REMS also include, in section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

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

N 022266 REMS ASSESSMENT

NEW SUPPLEMENT FOR N 022266
REMS ASSESSMENT
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR N 022266

REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

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

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

EXPIRATION DATING PERIOD

An expiry of 24 months is granted under the recommended storage conditions: Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature].

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

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, call Kimberly Compton, R.Ph., Regulatory Project Manager, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and
Rheumatology Products
Office of Drug Evaluation II
Center of Drug Evaluation and Research

Enclosures-

Package Insert
Medication Guide
Carton and Container Labeling
REMS
REMS Materials-

- Dear Prescriber Letter
- Healthcare Professional Program Overview
- Prescriber Enrollment Form (including Prescriber Knowledge Assessment)
- Website Educational Materials
- Printed Educational Materials
- Pharmacy Enrollment Form
- Dear Pharmacist Letter
- Patient Program Overview
- Patient Enrollment Form (including HIPPA Authorization)
- Wholesaler/Distributor Enrollment Form

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bob Rappaport

7/16/2009 11:02:24 AM