DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-266

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 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (fentanyl bioerodible mucoadhesive [redacted] oral transmucosal 200, 400, 600, 800, and 1200 mcg. b(4)

The Labeling and Nomenclature Committee (LNC) has determined that the appropriate established name for this product is fentanyl buccal soluble film.

We have reviewed the format of the package insert (PI) submitted with your application for compliance with the Physician's Labeling Rule (PLR) formatting rules. The Division of Drug Marketing, Advertising, and Communication (DDMAC) has completed their content review of the labeling. The Division of Medication Errors and Technical Support (DMETS) in the Office of Surveillance and Epidemiology (OSE) has reviewed your proposed carton and container label, [redacted] and proposed trade name. Based on these reviews, we have the following comments and recommendations. We request a prompt written response in order to continue our evaluation of your NDA. b(4)

1. The use of the trade name, Onsolis, is acceptable. However, if any of the proposed product characteristics are altered prior to the approval of the product, this assessment may be rescinded. Additionally, the proposed name will be re-evaluated 90 days prior to the PDUFA date for this application.

2. Regarding the **HIGHLIGHTS** section of the label

    a. Type size for all labeling information, headings and subheadings must be a minimum of 8 point type. This applies to Contents and the Full Prescribing Information (FPI) as well. [See 21 CFR 201.57(d)(6) and Implementation Guide.]

b. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]. The highlights presented in this draft of the label exceed the one-half page limit and are not presented in the two-column format. Revise your label to meet these requirements.

c. The "Initial U.S. Approval" date should list the year in which FDA initially approved the new molecular entity of fentanyl, the active ingredient in your product. For new formulations, the original date of approval of the active ingredient is used, even if the labeling does not refer to older formulations. Therefore,"20XX" cannot represent a correct initial US approval of fentanyl. Revise the date accordingly. (Sublimaze brand of fentanyl citrate injection, was first approved on February 19, 1968.)

d. A horizontal line must separate the Highlights, Contents, and Full Prescribing Information (FPI) [See 21 CFR 201.57(d)(2)]. Revise the formatting to insert such a line following Highlights and before Contents.

e. A revision date (i.e., "Revised: month/year") must appear at the end of the Highlights section. [See 21 CFR 201.57(a)(15)]. For a new NDA, the revision date should be left blank at the time of submission and will be edited to the month/year of application approval. You will need to revise this date accordingly, to reflect the date of approval of this supplement, but for now, it should remain blank.

f. Insert an actual phone number to which patients can call to report adverse reactions into your toll-free number place-holder in the Adverse Reactions section.

g. Remove the header from all pages of this document.

h. b(4)

i. For consistency with the *Use in Specific Populations-Pediatric Use* section of your proposed PI, we recommend including the important limitation to the indication that your product is for use only in patients 18 years of age and older in the *Indications and Usage* section.

j. For consistency with the *Use in Specific Population* section of your proposed PI, we recommend revising ' ' to read "Administer ONSOLIS with caution to patients with hepatic or renal impairment." b(4)

k. We recommend including information about ONSOLIS use in Labor and Delivery and Nursing Mothers for consistency with the *Use in Specific Populations* section of your proposed PI.

3. Regarding the **CONTENTS** section of the label

a. Use a two-column format for the Contents section, and if possible, limit the length to one-half page. Revise your label to meet these recommendations.

b. Headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10).] Revise your Contents to reflect these requirements.

c. In keeping with the headings and subheadings outlined in 21 CFR 201.56(d)(1), revise the title of subheading 9.3 to be only "Dependence", not "Physical Dependence and Withdrawal."

4. Regarding the **FULL PRESCRIBING INFORMATION (FPI)** portion of the label

a. In keeping with the headings and subheadings outlined in 21 CFR 201.56(d)(1), revise the title of subheading 9.3 to be only "Dependence", not '[redacted] b(4)

b. In the Contraindications section, only known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug) should be listed. If the contraindication is not theoretical, then it must be worded to explain the type and nature of the adverse reaction. Therefore, consider removing the statement "TRADENAME is contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl."

c. The manufacturer information (See 21 CFR 201.1) should be located after the Patient Counseling Information section, at the end of the labeling.

d. The '[redacted]statement appears at the end of your labeling. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to Medication Guides (MG). Revise your labeling to remove this statement from the PI. b(4)

e. Insert actual phone numbers to which patients can call to gain information on obtaining guides for Patients and Caregivers and to get additional assistance in disposing of excess, unusable units into your toll-free number place-holder the *Guide for Patients and Caregivers* (17.2) and *Disposal of Unneeded TRADENAME Units* (17.3) sections.

f. [redacted] b(4)

g. [redacted] b(4)

h. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.

i. [redacted] b(4)

j. As the Boxed Warning section of your proposed PI includes certain information about the drug's Dosage and Administration, specify that ONSOLIS doses must be separated by at least 2 hours, as similar language is in the Boxed Warning of the Fentora PI.

k. For consistency with the *Use in Specific Populations-Pediatric Use* section of your proposed PI, we recommend including the important limitation to the indication that your product is for use only in patients 18 years of age and older in the *Indications and Usage* section.

l. While your statement in the Contraindications section that '[redacted] b(4) may be accurate, it is promotional in tone and minimizes the risks of ONSOLIS therapy. Therefore, we strongly recommend deletion.

m. In the *Respiratory Depression* subsection of Warnings and Precaution it is appropriate to add the following additional language from the Warnings-Respiratory Depression section of the Fentora PI:

> Respiratory depression is the chief hazard of opioid agonists, including fentanyl, the active ingredient in TRADENAME. Respiratory depression is more likely to occur in patients with underlying respiratory disorders and elderly or debilitated patients, usually following large initial doses in opioid non-tolerant patients, or when opioids are given in conjunction with other drugs that depress respiration.
>
> Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with the 'sighing' pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide retention from opioid-induced respiratory

depression can exacerbate the sedating effects of opioids. This makes overdoses involving drugs with sedative properties and opioids especially dangerous.

n. For consistency with the Actiq PI, specify that the pain referred to in the following passage is actually cancer pain.

> Because the clinical trials of TRADENAME were designed to evaluate safety and efficacy…all patients were also taking concomitant opioids...such as…transdermal fentanyl, for their persistent pain. The adverse reaction data presented here reflect the actual percentage of patients…who received TRADENAME for breakthrough pain along with a concomitant opioid for persistent pain.

o. [redacted] b(4)

p. In the Description section, the claim [redacted] is promotional and overstates the efficacy of ONSOLIS. Delete it from the label. b(4)

q. In the *Pharmacokinetics* subsection of the Clinical Pharmacology section, there are multiple references to the product's "[redacted] While we acknowledge this drug product is used for breakthrough cancer pain (and thus would be expected to have a reasonable onset of action), use of the term [redacted] is unacceptable and must be removed. b(4) b(4)

5. Regarding the **MEDICATION GUIDE (MG)** portion of the label

a. Revise your MG so that the following is the first bullet under the heading "What is the most important information I should know about TRADENAME?"

[redacted] b(4)

b. To improve consumer comprehension, provide context for the terms "small" and [redacted] as used in the *What is TRADENAME?* section of your MG. b(4)

c. Provide justification as to why you have eliminated the phrase, [redacted] from the *What should I tell my doctor before starting TRADENAME?* section of your MG, while it appears in the Actiq and Fentora Med Guides, and replaced it with [redacted] Hallucinations are not the same as [redacted] and should not be used interchangeably. b(4)

If you cannot provide adequate justification, revise your MG to include the language present in the Actiq and Fentora Medication Guides instead.

d. Also in the *What should I tell my doctor before starting TRADENAME?* section of your MG, add language to include problems with drug abuse and addiction to the already listed problems with alcohol in order to maintain consistency with the *Drug Abuse and Dependence* section of the proposed PI as well as the Actiq and Fentora.

e. Specify that a '[redacted] of TRADENAME is [redacted] in the *How should I use TRADENAME?* section of your MG. b(4)

f. In the *How should I use TRADENAME?* section of your MG for consistency with the *Dosage and Administration* section of the proposed PI, include the following information:

   i. "ONSOLIS should only be used once per episode";
   ii. "ONSOLIS use should be limited to four or fewer episodes per day";
   iii. "Doses should be separated by at least two hours."

g. Regarding the instructions to [redacted] b(4)
[redacted] included as the last bullet of the *How should I use TRADENAME?* section of the MG, it may not be possible for the patient to follow the instructions if they are somnolent or have respiratory depression. Therefore, revise this statement to read as follows: "If you take too much ONSOLIS, you, your caregiver, or someone else nearby should call 911 for emergency help."

h. Add the additional common side effects of "disturbances in consciousness" and "neurological signs and symptoms" specified in the *Adverse Reactions* section of your proposed PI in consumer-friendly language to the "Common side effects include: nausea, vomiting, sleepiness, and dizziness." list in the [redacted] b(4)
[redacted] section of your MG.

i. Provide justification as to why you have excluded the following language from the [redacted]? section b(4)
of your MG which are found in the Actiq and Fentora MGs:

   1) **These symptoms may lead to serious problems or death if not treated right away.**

      a. **TRADENAME can cause your blood pressure to drop.** This can make you feel dizzy if you get up too fast from sitting or lying down.

      b. **TRADENAME can cause physical dependence.** Do not stop taking TRADENAME or any other opioid without talking to your doctor. You could become sick with uncomfortable

withdrawal symptoms because your body has become used to these medicines. Physical dependency is not the same as drug addiction.

2) Constipation (not often enough or hard bowel movements) is a very common side effect of pain medicines (opioids) including TRADENAME and is unlikely to go away without treatment. Talk to your doctor about dietary changes, and the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking TRADENAME.

If you cannot provide adequate justification for these deletions, revise your MG to include the above language from the Actiq and Fentora Medication Guides.

j. For consistency with the [redacted] section of your proposed PI, include the following statement in the *How should I dispose of unopened TRADENAME units when they are no longer needed?* section of your MG. b(4)

Repeat steps 1 and 2 for each unit; flush the toilet after all unneeded units have been deposited in the toilet.

6. The current labels of ONSOLIS inadequately address the safety issues with respect to use in appropriate patients, inappropriate substitution with other oral transmucosal fentanyl citrate products, and inappropriate dosing. Revise the labels and labeling for ONSOLIS to include appropriate warning and instructions to educate everyone involved in the medication use process, including prescribers, pharmacists, and patients/caregivers, regarding the risks associated with the use of ONSOLIS as noted below.

a. **CONTAINER LABEL**

1) Include the statements [redacted] and [redacted] in red font inside the boxed warning. b(4)

2) Revise the color scheme(s) used for the 600 mcg and/or 800 mcg so that the colors are more distinct from one another.

3) Include explicit dosing instructions on the container label specifically highlighting a maximum dose for a single breakthrough pain episode and the time needed between dosing for another breakthrough pain episode.

4) Include the net quantity (i.e., 1 system) on the container label.

b. **CARTON LABELING (28 UNITS AND 112 UNITS)**

1) See comments 1 and 2 in the CONTAINER LABEL section above.

2) Box the pharmacist checklist and relocate it to the principal display panel in order to increase its prominence.

3) Revise the first item in the pharmacist checklist to read [redacted] b(4)

4) Revise the second item in the pharmacist checklist to read [redacted] b(4)

5) Revise the font color of the first two items in the pharmacist checklist in order to increase their prominence (e.g., red font).

6) Per CFR 21 208.24(d), revise the fourth item in the pharmacist checklist to read "Instruct patients to read the enclosed ONSOLIS Medication Guide".

7) Revise the net quantity to read "XX units per carton".

[redacted] b(4)

Revise your labeling according to the recommendations listed above and amend your NDA with updated labeling by April 19, 2008.

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley, M.S.
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sara Stradley
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