Question 10
After NDA approval, what will be the process for modifying specific aspects of the FOCUS program?

FDA Response
After a REMS has been approved, any modification to the REMS will require the submission of a prior approval supplement identified as a "proposed REMS modification."

Question 11
As the REMS arena is rapidly evolving, does the Agency have any new REMS considerations related to FOCUS program for ONSOLIS?

FDA Response
Our advice provided in this document represents the most current Agency thinking on the application of REMS to product development.

Question 12
Is the previously submitted container and carton labeling acceptable?

FDA Response
The carton makes representation of the drug indication (e.g., first two check boxes for pharmacist include parts of the indication: opioid-tolerant and breakthrough pain) Therefore, we suggest including the most serious and most common risks with equal prominence. Additionally, we recommend that the warnings about possible fatality and risk to children from accidental exposure be as prominent as the indication claims.

Question 13
If ONSOLIS is approved, will the sponsor be responsible for alert and periodic reporting literature cases of adverse drug experiences for ONSOLIS only, all oral transmucosal fentanyl dosage forms and products, or all fentanyl dosage forms and products?

FDA Response
You will be responsible for adherence to the postmarketing regulations listed in 21CFR314.80.

Appendix A: REMS Template
If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name
Address
Contact Information

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

If a Communication Plan is included in the proposed REMS, include the following:

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Append the printed material and web shots to the REMS Document

C. Elements To Assure Safe Use

If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:
List elements to assure safe use included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:
A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS ;

C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);

D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;

E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or

F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

If an Implementation System is included in the proposed REMS, include the following:
Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

E. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments at a minimum must include an assessment by 18 months, 3 years, and in the 7th year after the REMS is initially approved, with dates for additional assessments if more frequent assessments are necessary to ensure that the benefits of the drug continue to outweigh the risks. We recommend that you specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. We recommend that assessments be submitted within 60 days of the close of the interval.

The second part of the submission should be a REMS Supporting Document that includes a thorough explanation of the rationale for, and supporting information about, the content of the Proposed REMS. This REMS Supporting Document should include the following listed sections 1 through 5, as well as a table of contents. Include in section 3 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary.

1. Background
2. Goals
3. Supporting Information on Proposed REMS Elements
    a. Additional Potential Elements
        i. Medication Guide
        ii. Patient Package Insert
        iii. Communication Plan
    b. Elements to Assure Safe Use
        i. include a statement on how the elements to assure safe use will mitigate the observed safety risk
    c. Implementation System

d. Timetable for Assessment of the REMS
4. Information Needed for Assessments
5. Other Relevant Information

In your Complete Response letter, prominently identify the Proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR NDA/BLA/ANDA [assigned #]
PROPOSED REMS

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

SUPPLEMENT [assigned #]
PROPOSED REMS – AMENDMENT

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

/s/

Kimberly Compton
11/12/2008 06:55:37 PM
CSO

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) submitted October 31, 2007, and received October 31, 2007, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Onsolis (fentanyl buccal soluble film) 200, 400, 600, 800, and 1200 mcg.

We also refer to our Complete Response Letter dated August 25, 2008, which included a marked-up copy of the labeling. The edits provided for the Medication Guide (MG) inadvertently omitted the changes suggested by the Office of Surveillance and Epidemiology (OSE). We apologize for this omission and have attached a revised marked-up version of the MG, showing the changes suggested to the MG by OSE.

The MG attached to this letter supercedes the one attached to our August 25, 2008 letter. When you submit your response to our August 25, 2008 letter, please include a MG revised as indicated in the attachment to this letter.

If you have any questions, call Kimberly Compton, 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 for Drug Evaluation and Research

Attachment

7 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Bob Rappaport
9/21/2008 08:53:43 PM