

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
12/17/2008 08:08:51 PM



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 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Onsolis (fentanyl buccal soluble film).

Attached are the Division's responses to the questions from your October ??, 2008, meeting package for our upcoming Post-Action Meeting, scheduled for November 17, 2008, to discuss issues related to our Complete Response letter dated August 25, 2008.

The previously agreed upon time is still set aside to meet with you, but, if you would like to either cancel the meeting, because you feel all your questions have been answered to your satisfaction, or re-focus the meeting (i.e., only focus on items which you feel require additional clarification), that would be acceptable to the Division as well. Alternatively, you can change the format of the meeting from face-to-face to teleconference. If you decide to change the format of the meeting, please contact us promptly by phone or e-mail.

We will be happy to provide clarification on any of the Division's responses, but **WILL NOT entertain any NEW questions, topics or review additional data** (there is simply not enough time prior to the meeting for the team to review such materials). Please let me know if you would like to change anything about our forthcoming meeting.

If you have any questions, call me at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEETING RESPONSES



Meeting Date: November 17, 2008

Time: 11:00 AM EST

Location: White Oak, Building 22, Conference Room 1313

Application: NDA 22-266

Regulatory Status: Complete Response Letter issued in 1st Review Cycle

Product: ONSOLIS (fentanyl buccal soluble film)

Proposed Indication: the management of breakthrough pain in patients with cancer, 18 years of age and older, who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

Sponsor: BioDelivery Sciences International, Inc. (BDSI)

Type of Meeting: Type A- Post-Action Meeting

Meeting Chair: Sharon Hertz, M.D., Director

Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

Minutes Recorder: Kimberly Compton, Project Manager, DAARP

BDSI Representatives	Title
David T Wright, Ph.D., RAC	Director, Regulatory Affairs, BDSI
Andrew L Finn, Pharm.D.	Executive Vice President, Clinical Product Development, BDSI
David Blum, M.D.	Vice President, Clinical Research and Medical Affairs, BDSI
Mark A Sirgo, Pharm.D.	President and Chief Executive Officer, BDSI
_____	_____
_____	_____
Harry J Sacks, M.D.	Vice President, Medical and Scientific Affairs, Meda Pharmaceuticals Inc.
Richard N Spivey, Pharm.D., Ph.D.	Vice President, Development Meda Pharmaceuticals Inc.
_____	_____
Sharon S Clarke	President, Meda Pharmaceuticals Inc.
FDA	Title
Bob Rappaport, M.D.	Director, Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Sharon Hertz, M.D.	Deputy Director, DAARP
Ellen Fields, M.D., M.P.H.	Medical Team Leader, DAARP
Larissa Lapteva, M.D.	Deputy Director for Safety, DAARP
Dominic Chiapperino, Ph.D.	Safety Regulatory Project Manager, DAARP
Mary Dempsey	Risk Management Programs Coordinator, Division of Risk Management (DRISK), Office of Surveillance and Epidemiology (OSE)
Mary Willey, Ph.D.	Acting Team Leader, Risk Management Analysts, DRISK, OSE
Kristina Arnwine, Pharm.D.	Team Leader, Division of Medication Error Prevention and Analysis (DMEPA), OSE
Afrouz Nayernama, PharmD	Safety Evaluator, Division of Pharmacovigilance (DPV) I, OSE
Agnes Plante	Office of Compliance
LT Mathilda Fienkeng, Pharm.D.	Senior Regulatory Review Officer, Division of Drug Marketing, Advertising and Communication (DDMAC)
Jodi Duckhorn, MS	Team Leader, Patient Labeling and Education, DRISK, OSE
Brian Jordan, MS	Social Scientist, Patient Labeling and Education, DRISK, OSE
Kim Compton	Regulatory Project Manager, DAARP

b(4)

b(4)

Question 3

Is the proposed FOCUS facilitated distribution plan (Section 6.3) acceptable?

FDA Response

Provide additional detail regarding the following components of your proposed distribution plan:

- 1. The mechanics of the pharmacy prescription verification process and how this process relates to/interacts with the use of the “FOCUS Registry Database”**
- 2. Patient discontinuation procedures – these procedures are necessary in order to establish the population of subjects who are receiving treatment at any time**
- 3. Patient lost-to-follow-up procedures – these procedures are necessary in order to establish the population of subjects who are receiving treatment at any time**
- 4. Patient re-enrollment procedures (if a patient discontinues Onsolis and restarts) and any reasons to deny re-enrollment**
- 5. Program compliance monitoring and non-compliance procedures**
 - a. We note that “6.4.4 Intervention Plan” outlines the general approach. Describe the program monitoring activities to be employed to detect non-compliance with prescribers and pharmacies, and the “escalating safety communication plan.”**
 - b. The Prescriber Enrollment Form includes “site audits.” Describe the site audit components.**
- 6. The anticipated time to fill, dispense and receive an Onsolis prescription from the time the prescriber writes/faxes the prescription to patient receipt.**
- 7. The mechanics, cost and timing of the hard copy prescription “courier” process.**
- 8. In-patient hospital use (and distribution to hospitals)**

Question 4

Is the proposed plan for FOCUS prescriber training and enrollment (Section 6.3.1), including retraining and re-enrollment, acceptable?

FDA Response

We have the following comments on prescriber, pharmacy training and enrollment:

- 1. Any personal training conducted on behalf of BDSI must be provided by clinical professionals who do not have any responsibility for promotional or sales activities,**

including sales representatives, and whose compensation is not related to increasing sales of Onsolis.

2. All training/educational materials must be appended to the REMS template at the time of submission. All REMS materials must be consistent with product labeling, must not be misleading and must not be promotional.
3. We cannot comment on the acceptability of the proposed retraining component of the prescriber and pharmacy enrollment in the absence of further details regarding the process (how will retraining occur, what will retraining consist of, etc.).
4. Page 28 states, “ _____”

b(4)

Question 5

Is the proposed plan for FOCUS patient training and enrollment (Section 6.3.2) acceptable?

FDA Response

Regarding patient enrollment:

1. Describe the purpose of collecting the last four digits of a patient’s social security number as part of patient enrollment.
2. The meeting package and proposed Patient Enrollment Form include no information regarding sharing, disclosing and protecting patient health information. The program must include adequate controls to protect personal health information and to inform patients that health information will be shared and disclosed and protected.
3. All training/educational materials must be appended to the REMS template at the time of submission. All REMS materials must be consistent with product labeling, and must not be misleading or promotional.
4. Describe how patients will be discontinued from and/or re-enrolled into the program, etc.

Question 6

Is the proposed plan for FOCUS pharmacist training and enrollment (Section 6.3.4), including retraining and re-enrollment, acceptable?

FDA Response

- 1. Provide the specifics of tracking materials and all other elements of this section.**
- 2. Provide the details of timing of medication delivery to patients and any information regarding added costs, and any other relevant information.**
- 3. Propose triggers that prompt patient re-counseling.**
- 4. Provide the details on how “glitches” that might prevent dispensing will be addressed and the timing for addressing these interventions.**
- 5. Define the “network” of pharmacies (does this include chains such as CVS, etc.?)**
- 6. See response to Question 4 above.**

Question 7

Is the proposed plan for FOCUS prescriber confirmation of patient opioid tolerance and pharmacist counseling regarding the importance of opioid tolerance and other conditions for safe use (Section 6.3.1.1.6) acceptable?

FDA Response

The proposed plan appears appropriate, although we need to see the final program before providing further comment.

While we expect that the definition of opioid tolerance will be included in the educational materials, it would be useful to include this definition on the enrollment forms for prescribers, patients and pharmacies, as provided in Appendices 4, 5 and 6. This will underscore the requirement for opioid tolerance and help prevent drift in the standards used by all involved to define opioid tolerance.

Question 8

Is the proposed FOCUS implementation system (Section 6.4), including performance metrics as well as audit and reporting plans, acceptable?

FDA Response

Provide information about any potential gaps in therapy related to the procedures for dispensing the drug or any reports of gaps once the program is initiated. Provide templates of letters to be sent to possible REMS violators.

We note in Section 6.4.2, in the paragraph describing the distribution and prescription data monitoring plan, the following sentence: “This enables more effective control and eliminates the need for monitoring.” It is not entirely clear what is meant by this in the context that, without monitoring, one would not know if the program was working as planned. Clarify what monitoring might be suitable for elimination and how the lack of information gained via such monitoring will be otherwise collected or known.

Question 9

Is the proposed FOCUS assessment plan (Section 6.6) acceptable?

FDA Response

Include a plan to evaluate the utilization patterns among opioid non-tolerant patients. Provide more details regarding the planned surveys, including the frequency of the surveys.

Submit a plan to evaluate the prescribers’ and patients’ understanding of the safe use of ONSOLIS and the FOCUS program. Include the following:

All methodology and instruments used to evaluate the prescribers’ and patients’ understanding of the safe use of ONSOLIS and the FOCUS program. This should include, but not be limited to:

- 1. The sample size and confidence limits associated with that sample size**
- 2. How the sample will be determined (selection criteria)**
- 3. The expected number of patients/physicians surveyed**
- 4. How the participants will be recruited**
- 5. How and how often the surveys will be administered**
- 6. An explanation of the controls used to minimize bias**
- 7. An explanation of the controls used to compensate for the limitations associated with the methodology**
- 8. The survey instruments that will be used for review (e.g., questionnaires and moderator's guide).**
- 9. Any background information on testing survey questions and their correlation to the educational materials.**