Question 2
Is the proposed FOCUS communication plan (Section 6.2) acceptable?

FDA Response
The proposed plan to identify the target prescriber population appears acceptable.

Move the materials listed in the proposed Communication Plan to the corresponding Elements to Assure Safe Use section. (i.e., prescribers section, pharmacies section)We note that none of the materials listed in this section are provided and remind you that all REMS materials (enrollment forms, educational materials, website, call center scripts, letters) must be appended to the REMS template in final mock-up format with graphics, etc, at the time of submission. All REMS materials must be consistent with product labeling and must not be misleading or promotional.

Discussion
There was no further discussion of this question.

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)**

Discussion
The sponsor clarified that once patients enroll they are never unenrolled. Once enrolled, **patients may be "activated" after meeting all safe use conditions for dispensing. Patients can be "inactivated" for a variety of reasons (e.g.,** lost to follow-up, reports of abuse or misuse, etc.). If a prescriber wants to reactivate the patient, then the sponsor will pass on the reasons for inactivation of the patient and let the prescriber decide if the patient should be reactivated (practice of medicine issue.)

The sponsor stated that the REMS vendor will monitor prescribers and those with inappropriate patterns of prescribing will be contacted and an escalating intervention ladder may be followed if necessary that can lead to inactivation of the prescriber from further participation in the FOCUS Program.

The Agency agreed that this was a reasonable approach.

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** [redacted] b(4)

b(4)

Discussion
The sponsor clarified that there will be no training or presentations conducted by sales representatives, noting that REMS information will be provided in one of the following ways:

1.

2. b(4)

3.

The sponsor estimated tha[redacted] b(4)

The Agency suggested that combining a quiz (e.g., 5 to 10 questions related to key aspects of the FOCUS Program training such as the definition of opioid tolerance) with the enrollment form would address the Agency concerns that sales representatives will not be training or influencing the prescribers and that prescribers will have actually undertaken the training and understand the important messages about the product. Dr. Rappaport emphasized that the prescribers should not be provided the correct answers by representatives and that the quiz should be graded, with the prescriber needing to get the responses correct before being allowed to enroll patients. It was agreed that these same questions could be included as part of the KAB (Knowledge, Attitude and Behavior) surveys.

The sponsor summarized this issue by stating that all the discussed routes are potentially do-able and noted that the Agency's concern on this point lies mainly with demonstrating that the prescribers know and understand the important safety issues involved with the use of this product. The sponsor stated that they will take this under advisement and will also need to assess the performance based on the route by which the prescriber was trained.

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.**

Discussion
There was no further discussion of this question.

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.**

Discussion
The sponsor stated that if a patient is inactivated for any reason, in order to reactivate, they will need to start again, i.e., they will receive complete retraining that will address all topics covered during initial training. The sponsor clarified that patients will be retrained under three circumstances:

1. Reactivation after inactivation;

2. Changes to relevant sections of the prescribing information (black box, warnings and precautions); or

3. Every 2 years.

The sponsor explained that reasons for inactivation would include (but not be limited to: loss to follow-up, failure to obtain a continuation prescription for an interval of time (≥3 months), or reports of abuse or misuse).

The Agency indicated that this proposal sounds reasonable.

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.

Discussion
Dr. Hertz clarified that the system should have checks and balances to try to avoid drift, i.e., moving away from the important risk messages such as selection of opioid-tolerant patients. It was noted that in the current form, the assessment of the patient's opioid tolerance is not a responsibility of the pharmacist.

The sponsor pointed out that under this proposed model, the pharmacist is remote and would not have access to any patient data to confirm opioid tolerance and the pharmacist would only be able to access on any patient- or caregiver-reported information which has the potential to be unreliable. The sponsor further commented that it is part of the practice of

medicine for the prescriber to determine if the patient is opioid-tolerant but not in the normal practice of the pharmacist.

Dr. Hertz stated that the Agency would consider the firm's arguments and would address them in a post-meeting note. The firm stated that they would submit this argument via email for follow-up.

**<u>Post-Meeting Note-</u>

The Division agrees that the determination of a patient's status regarding opioid tolerance is best made by the prescriber, and is beyond the usual scope of the dispensing pharmacist's practice. However, if the assessments of the REMS over time show that prescriptions are being dispensed to non-opioid tolerant patients, additional measures such as a system where information regarding opioid tolerance is communicated from the prescriber to the dispensing pharmacist and is a required element for the product to be dispensed may need to be implemented.

Question 8
Is the proposed FOCUS implementation system (Section 6.4), including performance metrics as well as audit and reporting plans, acceptable?

<u>FDA Response</u>
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: '[redacted] 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.

b(4)

<u>Discussion</u>
There was no further discussion of this question.

Question 9
Is the proposed FOCUS assessment plan (Section 6.6) acceptable?

<u>FDA Response</u>
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.**

Discussion
The sponsor requested clarification about the term controls as stated in the responses above. The sponsor clarified that the survey sample is drawn from prescribers and patients who are enrolled in the FOCUS Program and so it was not apparent what other prescribers or patients could be utilized as controls in an appropriate fashion.

Dr. Willy stated that she believed the term controls refers to survey methods used to minimize bias rather than prescriber/patient controls, but also noted that she would confirm this. It was agreed that stratification by age and gender seemed appropriate, but Dr. Willy indicated that she would confirm this interpretation with the relevant Agency personnel and include a post-meeting note.

****Post-Meeting Note-**

Dr. Willy confirmed that the Agency needs to know what methods will be used to minimize bias. The sponsor should also clarify how the limitations for bias will be compensated for in their methodology. In addition, stratification by age and gender are appropriate.

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."

Discussion
There was no further discussion of this question.

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.

Discussion
There was no further discussion of this question.

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.

Discussion
The sponsor stated that two questions had been sent by email without enough time for the Agency to respond before the meeting and inquired if the Agency could respond during the meeting.

The two questions were:

1. *Would it address the Agency comments if BDSI changed the container and carton label warning text as follows?*

[redacted] b(4)

b(4)

The sponsor stated that they made the front and back panels of the carton labels identical to ensure that the important information would always be visible even once a pharmacy label was placed on the carton. The firm stated that the Rx checklist is required and that they had received comments on it during the review cycle.

The sponsor stated that they would provide suggested changes to the proposed carton and container labeling as soon as possible.

**__Post-Meeting Note-__

There are warnings in the section of the carton directed towards patients and warnings directed to prescribers and dispensers rather than patients that are duplicative and cause clutter on the carton. This should be simplified so that a larger font can be used and the carton is easier to read for both pharmacists and patients. We would like to review any revisions to the container label and carton labeling.

2. *Does the Agency have any comments related specifically to the container label, i.e., individual foil package label?*

The sponsor stated that they do not believe it is possible to address all the possible risks in the limited space available.

Dr. Hertz stated that the Agency will have additional comments on the labeling, even outside the meeting, but could not predict when those might be ready to issue.

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.

__Discussion__
There was no further discussion of this question.

Closing Discussion:
The sponsor stated that they took the messages of public safety seriously and were committed to address these concerns. The firm stated that they believed they would be able to address the Agency's concerns about the currently proposed REMS and would carefully review the meeting discussions internally, but might expect to send the NDA resubmission as early as November 26, 2008.