

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207932Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 207932
Product Name: Belbuca (buprenorphine)

PMR/PMC Description: A multiple ascending dose clinical trial in adults to determine the maximum tolerated dose of buprenorphine without co-administration of naltrexone to inform the dosing for a thorough QT (tQT) trial of buprenorphine.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	04/2016
	Study/Trial Completion:	04/2017
	Final Report Submission:	10/2017
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Another buprenorphine product with a similar clinical pharmacologic profile is currently marketed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The data from the Phase 3 trials are sufficient to indicate that Belbuca, in the proposed dose range, may result in QT prolongation. The goal is to evaluate the effects of Belbuca on cardiac repolarization in a thorough QT trial and to provide additional information to assess the safety of Belbuca, which may lead to additional labeling.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A multiple ascending dose clinical trial in adults to determine the maximum tolerated dose of buprenorphine without co-administration of naltrexone to inform the dosing for a thorough QT (tQT) trial of buprenorphine.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-

- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 207932
Product Name: Belbuca (buprenorphine)

PMR/PMC Description:

A thorough QT trial in adults without naltrexone co-administration to assess the risk of QT prolongation with buprenorphine. This trial will provide information on the conduction effects of buprenorphine on the heart, specifically cardiac repolarization, at therapeutic and suprathreshold dose regimens. The tQT trial may be conducted as part of the multiple ascending dose trial.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>07/2017</u>
	Study/Trial Completion:	<u>07/2018</u>
	Final Report Submission:	<u>01/2019</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Another buprenorphine product with a similar clinical pharmacologic profile is currently marketed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The data from the Phase 3 trials are sufficient to indicate that Belbuca, in the proposed dose range, may result in QT prolongation. The goal is to evaluate the effects of Belbuca on cardiac repolarization in a thorough QT trial and to provide additional information to assess the safety of Belbuca, which may lead to additional labeling.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A thorough QT trial in adults without naltrexone co-administration to assess the risk of QT prolongation with buprenorphine. This trial will provide information on the conduction effects of buprenorphine in the heart, specifically cardiac repolarization, at therapeutic and suprathreshold dose regimens. The tQT trial may be conducted as part of the multiple ascending dose trial.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-

- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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

/s/

SPIROS NICOLS
10/23/2015

JUDITH A RACOOSIN
10/23/2015

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # ER/LA opioid analgesics, with the addition now of NDA 207932
Product Name: Belbuca (buprenorphine)

PMR/PMC Description: Conduct one or more studies to provide quantitative estimates of the risks of misuse, abuse, addiction, overdose and death associated with long-term use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid products. Include an assessment of risk relative to efficacy.

These studies should address at a minimum the following specific aims:

- I. Estimate the incidence of misuse, abuse, addiction, overdose, and death associated with use long-term use of opioids for chronic pain. Stratify misuse and overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, addiction, overdose, and death.
 - II. Evaluate and quantify other risk factors for misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify misuse and overdose by intentionality wherever possible.
-

PMR/PMC Schedule Milestones:	Final Protocol Submission:	08/2014
	Study/Trial Completion:	01/2018
	Final Report Submission:	06/2018
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval

- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

In order to estimate the incidence of misuse, abuse, addiction, overdose, and death associated with use long-term use of opioids for chronic pain, we must be able to access data from adequate numbers of patients who were treated long-term with opioids.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of opioids, including misuse, abuse, addiction, overdose and death. The goal of the study is to determine those incidences, and identify risk factors for those outcomes.

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study:** all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial:** any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The initial type of study that would be anticipated would be an epidemiological study in large databases to measure the incidences of the adverse outcomes listed above. However, the codes for these outcomes have not been validated. As such, validation studies are required prior to the epidemiological studies (see other PMRs). It may be determined, if the outcome codes do not validate well, that other types of studies or clinical trials are needed.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)

- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # ER/LA opioid analgesics, with the addition now of NDA 207932 for Belbuca
Product Name:

PMR/PMC Description: Develop and validate measures of the following opioid-related adverse events: misuse, abuse, addiction, overdose and death (based on DHHS definition, or any agreed-upon definition) , which will be used to inform the design and analysis for PMR # 2065-1 and any future post-marketing safety studies and clinical trials to assess these risks. This can be achieved by conducting an instrument development study or a validation study of an algorithm based on secondary data sources.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	08/2014
	Study/Trial Completion:	08/2015
	Final Report Submission:	11/2015
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The data needed to validate measures of opioid-related adverse events would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of opioids, including misuse, abuse, addiction, overdose and death. The goal of the study is to determine those incidences, and identify risk factors for those outcomes.

In order to conduct such a study, the outcomes need to be validated, including measures of opioid-related adverse events.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An observational study would likely be conducted that includes identifying patients who fulfill a measure of the opioid-related adverse event, and then conducting chart review or a similar activity to determine whether the identified patients actually meet the case definition.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # ER/LA opioid analgesics, with the addition now of NDA 207932 for Belbuca
Product Name: _____

PMR/PMC Description: Conduct a study to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the following opioid-related adverse events: misuse, abuse, addiction, overdose, and death in any existing post-marketing databases to be employed in the studies. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>08/2014</u>
	Study/Trial Completion:	<u>08/2015</u>
	Final Report Submission:	<u>11/2015</u>
	Other: _____	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The data needed to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the opioid-related adverse events: misuse, abuse, addiction, overdose, and death would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of opioids, including misuse, abuse, addiction, overdose and death. The goal of the study is to determine those incidences, and identify risk factors for those outcomes.

In order to conduct such a study, the coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify opioid-related adverse events: misuse, abuse, addiction, overdose, and death need to be validated.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
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Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An observational study would likely be conducted that includes identifying patients using coded medical terminologies (e.g., ICD9, ICD10, SNOMED) for opioid-related adverse events: misuse, abuse, addiction, overdose, and death, and then conducting chart review or a similar activity to determine whether the identified patients actually meet the clinical definition.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
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- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
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- Other
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5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
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PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

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- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An observational study would likely be conducted that includes identifying patients who fulfill a measure of “doctor/pharmacy shopping”, and then conducting chart review or a similar activity to determine whether the identified patients actually meet the case definition.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # ER/LA opioid analgesics, with the addition now of NDA 207932 for Belbuca
Product Name: _____

PMR/PMC Description: Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following use of ER/LA opioid analgesics for at least one year to treat chronic pain. We strongly encourage you to use the same trial to assess the development of tolerance following use of ER/LA opioid analgesics. Include an assessment of risk relative to efficacy.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>08/2014</u>
	Study/Trial Completion:	<u>08/2016</u>
	Final Report Submission:	<u>02/2017</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

In order to estimate the risk for the development of hyperalgesia following use of opioid analgesics for at least one year, we must be able to access data from adequate numbers of patients who were treated long-term with opioids.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of serious adverse effects of opioids, including hyperalgesia. The goal of the trial is to determine the risk of developing hyperalgesia.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A clinical trial is needed to determine the risk of hyperalgesia following long-term treatment with opioids because this condition can be distinguished most easily with a randomized withdrawal design.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

SPIROS NICOLS
10/23/2015

JUDITH A RACOOSIN
10/23/2015

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 207932
Product Name: Belbuca (buprenorphine)

PMR/PMC Description: Conduct an open- label study to evaluate the pharmacokinetics and safety of Belbuca in patients 7 through 16 years.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/2016</u>
	Study/Trial Completion:	<u>06/2022</u>
	Final Report Submission:	<u>12/2022</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Product is ready for approval in adult population

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

To satisfy Pediatric Research Equity Act requirements

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An open-label study evaluating safety and pharmacokinetics in patients 7 through 16 years of age
--

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs? Yes

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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/s/

SPIROS NICOLS
10/23/2015

JUDITH A RACOOSIN
10/23/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Pediatric Labeling Review

From: Amy M. Taylor, MD, MHS Medical Officer
Division of Pediatric and Maternal Health

Through: Hari Cheryl Sachs, MD, Team Leader
Division of Pediatric and Maternal Health

Linda L. Lewis, MD, Acting Deputy Director
Division of Pediatric and Maternal Health

NDA Number: 207-932

IND Number: 72,428

Sponsor: Endo Pharmaceuticals, Inc.

Drug: Belbuca™ (buprenorphine hydrochloride) buccal film

Dosage form and route of administration: buccal film, oral

Indication: For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate

Consult request: The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requests DPMH’s input on the proposed labeling for Belbuca™ buccal film.

Background

The sponsor submitted an original NDA (207-932) on December 23, 2014. The sponsor submitted an initial Pediatric Study Plan (iPSP) on July 25, 2014. FDA did not initially

agree with the iPSP. However, an agreed PSP was established on February 5, 2015 prior to the filing date. (b) (4)

Reviewer comment: During the review by the Pediatric Review Committee (PeRC), the PeRC recommended that the age cut-off for the waiver of PREA required studies be decreased to 2 or 4 years of age.

Sponsor proposed labeling

8.4 Pediatric Use

(b) (4)

Proposed DAAAP edits to labeling

(b) (4)

8.4 Pediatric Use

The safety and efficacy of BELBUCA [have](#) not been established in [pediatric patients](#). (b) (4)

DPMH Recommendations:

The statement in Highlights Use in Specific Populations is not necessary. The absence of information is usually not included in the Highlights section. In addition, the statement implies (b) (4). DPMH recommends that the statement be removed.

DAAAP's proposed changes to subsection 8.4 are acceptable.

These recommendations were communicated to DAAAP during labeling meetings. Labeling negotiations are ongoing. The final labeling may differ as a result of those negotiations (see approval letter).

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/s/

AMY M TAYLOR
10/20/2015

HARI C SACHS
10/20/2015
I agree with these labeling recommendations.

LINDA L LEWIS
10/20/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, Office of Drug
Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: September 24, 2015 **Consult Received:** March 2, 2015

From: Carol H. Kasten, MD, Medical Officer
Division of Pediatric and Maternal Health, Maternal Health Team
Office of Drug Evaluation IV (ODE IV)

Through: Tamara Johnson, MD, MS, Acting Team Leader
Maternal Health Team
Division of Pediatric and Maternal Health, ODE IV

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health, ODE IV

To: Division of Analgesia, Anesthesia and Addiction Products

Drug: Belbuca (buprenorphine) buccal film
Schedule III Controlled Substance

Sponsor: Endo Pharmaceuticals Inc.

Proposed Indication: Belbuca is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Subject: PLLR labeling for a new extended release/long acting (ER/LA) opioid drug product

Consult Request: "DAAAP needs input from DPMH for appropriately labeling the product, including risk summary for specific populations."

Documents Reviewed: Endo Pharmaceuticals, Inc. application documents; PMHS-MHT Review (b) (4) (buprenorphine-naloxone) sublingual tablet; NDA 204 442, Primary Author: Leyla Sahin, MD; dated June 7, 2013.

INTRODUCTION

Endo Pharmaceuticals, Inc. submitted this 505(b)(2) application on December 23, 2015 identifying the Reference Listed Drug (RLD) as buprenorphine sublingual (SL) tabs, (ANDA 78-633), Roxane Laboratories.¹ The indication for the RLD is treatment of opioid addiction, one of two indications that have been approved for buprenorphine containing drugs. The other approved indication for buprenorphine is treatment of pain. For this NDA, the applicant is only seeking approval for use of Belbuca as an extended release/long acting (ER/LA) opioid to manage pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. This consult will review only those buprenorphine data and publications which are related to the Belbuca indication of pain management, not opioid dependence. On March 2, 2015 the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Division of Pediatric and Maternal Health Staff - Maternal Health Team (DPMH-MHT) to review and provide labeling recommendations for the Belbuca Warning and Precautions, Pregnancy and Lactation subsections.

BACKGROUND

Brief Regulatory History

The IND (IND 72-428) for this buprenorphine film formulation was submitted in December, 2005 by BioDelivery Sciences International, Inc (BDSI). The application was transferred to Endo Pharmaceuticals, Inc. on January 6, 2012. In subsequent communications, the Agency agreed that the relative bioavailability studies submitted were acceptable and no new nonclinical studies would be required as the buprenorphine exposure from the maximum recommended daily dose (MRDD) of Belbuca of 1800 mcg/day was lower than that approved for the RLD.

The first buprenorphine containing drug, Buprenex (NDA 20-733) was an immediate release formulation approved in 1981 for parenteral administration for treatment of moderate to severe pain. The next buprenorphine containing drug approved for pain management was Butrans (NDA 21-306), an ER/LA opioid approved in June, 2010.

Drug Characteristics

Buprenorphine has poor bioavailability when administered orally due to first-pass metabolism following gastrointestinal absorption. Consequently buprenorphine containing products are administered parenterally (Buprenex), sublingually as a tab (Subutex, NDA 20-732), buccal film (Suboxone film, NDA 20-733) or transdermally (Butrans). Buprenorphine is 96% protein bound and in the Belbuca formulation the buprenorphine half-life is 27 hours \pm 11.2 hours. The CYP3A4 isoenzyme metabolizes buprenorphine via N-dealkylation to an active metabolite, norbuprenorphine.

The Belbuca formulation is a water soluble, polymeric film applied to the buccal mucosa which releases buprenorphine as the film dissolves. The buccal film developed by BioDelivery Sciences International uses 'BioErodible MucoAdhesive (BEMA®) delivery

¹ Subutex (NDA 20-732) was not used as it was discontinued at the time the bioavailability studies were completed.

technology² and is the same formulation as that approved for use with Bunavail (NDA 205-637) in June, 2014. The Agency agreed, therefore, that no further excipient testing was required for approval.

Mechanism of Action

Buprenorphine is a partial agonist for the mu opioid receptors and a full antagonist for the kappa receptors.^{3,4} Binding of the mu receptor produces supraspinal analgesia, respiratory depression, euphoria and physical dependence. As a partial mu opioid agonist, buprenorphine reaches a maximal analgesic effect above which no analgesia is induced. One source⁵ states a 0.2 mg buprenorphine dose will induce analgesia and sedation whereas a dose of 20 mg will produce an opioid antagonist effect which may induce withdrawal in a patient who is opioid dependent. This 'ceiling effect' also limits the maximal respiratory depression induced.^{6,7}

Extended Release/Long Acting Opioid Analgesic Drug Products' Class Labeling

Opioid analgesic drug products which are Schedule II or III controlled substances with extended release or long acting (ER/LA) formulations indicated for the management of pain have required class labeling.⁸ As part of the class labeling, boxed warnings are required for addiction, abuse and misuse, respiratory depression that can lead to overdose and death and Neonatal Opioid Withdrawal Syndrome (NOWS) which may be life threatening in neonates whose mothers required prolonged opioid therapy while pregnant. In addition to the boxed warnings, there is class labeling in several sections and sub-sections. In April, 2014, the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS-MHT)⁹ recommended specific labeling for NOWS as part of a response to a Citizen's Petition on NOWS. The basis for the NOWS class labeling is contained in the April, 2014 PMHS-MHT consult review.¹⁰

Published Literature - Buprenorphine Use in Pregnancy and Lactation

While the indication for Belbuca is treatment of pain, this reviewer could find no publications on the use of buprenorphine for analgesia during pregnancy or lactation. The data on buprenorphine use during pregnancy and lactation are derived from studies in which the drug is used as an alternative to methadone for the treatment of opioid

² Applicant document NonClinical Overview

³ Clinical pharmacology online©, www.clinicalpharmacology-ip.com Elsevier. Gold Standard. Revision date: July 1, 2015. Accessed August 30, 2015.

⁴ Belbuca labeling August 27, 2015 version.

⁵ Kosten TR, Haile CN. Opioid-Related Disorders. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 19e. New York, NY: McGraw-Hill; 2015. <http://accessmedicine.mhmedical.com/content.aspx?bookid=1130&Sectionid=79757372>. Accessed August 31, 2015.

⁶ See Belbuca labeling.

⁷ See Kosten, *et al.*

⁸ *Draft Guidances for Industry: Analgesic Indications: Developing Drug and Biological Products (February 2014); and, Abuse Deterrent Opioids-Evaluation and Labeling (January 2013).*

⁹ PMHS-MHT was reorganized and re-named on October 1, 2014 as DPMH.

¹⁰ Co-Primary Authors Leyla Sahin, MD, Amy Taylor, MD, MHS. *Citizen Petition and Petition for Stay regarding Neonatal Opioid Withdrawal Syndrome (NOWS) labeling changes.* April 11, 2014. DARRTS Reference ID: 3488324

dependence in pregnant women. The buprenorphine doses used to treat opioid dependence are much higher than that requested for Belbuca. Specifically, the MRDD for Belbuca is 1.8 mg, whereas that for the RLD is 24 mg (doses above this demonstrated no clinical advantage). Data from studies using buprenorphine to treat opioid dependence during pregnancy would reflect drug doses many times higher, depending on the drug formulation used, than that recommended for Belbuca. In addition, the two patient populations, pregnant women with chronic pain and those who are opioid dependent, have different pregnancy risks and outcomes based on the underlying disorder being treated. Therefore, pregnancy exposure data from current publications on use of buprenorphine to treat opioid dependence during pregnancy will not be reviewed.

In reference to previous DPMH/PMHS reviews, a previous PMHS consult from June, 2013 contains a review of the considerable body of literature¹¹ on buprenorphine treatment for opioid dependence during pregnancy and lactation. The PMHS consult reviewed a randomized, controlled trial (RCT) comparing NOWS outcomes in pregnant women treated with buprenorphine to those treated with methadone, two very small RCTs, many observational studies with prospective data collection and several case series and reports. The lactation studies were more limited and included two studies on a total of 13 lactating women being treated with buprenorphine for opioid dependence.

The key findings from that review are:

- Prenatal buprenorphine exposure has not been found to increase the risk of congenital malformations.
- No dose-response relationship appeared to exist between maternal buprenorphine dosage and the incidence of NOWS.
- Buprenorphine is present in breast milk at very low levels; however, no adverse reactions have been demonstrated in a breastfed infant whose mother is being treated with buprenorphine.¹²

Since completion of the PMHS review in June, 2013 there have been no new RCTs or population-based studies to provide additional information for the Belbuca labeling.

Reviewer's Comment:

(b) (4)

(b) (4) *This reviewer recommends that further labeling decisions for buprenorphine containing products be postponed until such time as the (b) (4) labeling is revised to include the new data. If any of the new data are derived from use of these buprenorphine containing drugs as*

¹¹ PMHS Review of (b) (4) (NDA 204 442), Primary author Leyla Sahin, MD. Dated June 7, 2013. DARRTS Reference ID: 3321733.

¹² See (b) (4) review by Leyla Sahin, MD.

analgesics, then this information should be considered for addition to the Belbuca labeling.

Database Reviews – Reproductive and Lactation Exposures

As above, the studies on which the reproductive and lactation databases' reviews are based are derived from treatment of pregnant women with opioid dependence, not those in chronic pain. These database reviews are included here for completeness. The reproductive toxicology database, Reprotox,¹³ review notes that prenatal buprenorphine treatment for opioid dependence has been reported in several clinical studies. Based on animal studies, the review states that buprenorphine is not expected to increase the risk of adverse outcomes; however, the possible long-term effects of such treatment are not known. TERIS¹⁴ did not review the effects of prenatal use of buprenorphine. The lactation toxicology database, LACTMED®,¹⁵ summarizes pertinent findings on use of buprenorphine in lactating women: levels of buprenorphine in breastmilk are low, oral bioavailability for the breastfed infant is low and levels of buprenorphine in the serum and urine of breastfed infants are low. The LactMed review concludes that breastfeeding in women being treated with buprenorphine for opioid dependence is acceptable.

LABELING

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,”¹⁶ also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule¹⁷ format to include information about the risks and benefits of using these products during pregnancy and lactation.

There are no publications which may be used to inform the Belbuca Pregnancy labeling on use of buprenorphine for analgesia in pregnant women. The studies of opioid

¹³ Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed May 5, 2015.

¹⁴ TERIS is the TERatology Information Service located at University of Washington. It is an online database designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women.
http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/ Accessed 3/21/2014

¹⁵ LACTMED®: The LactMed database is a National Library of Medicine database with information on drugs and lactation geared toward healthcare practitioners and nursing women. LactMed Record Number: 990; Last Revision Date: 20130907

¹⁶ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

¹⁷ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

dependence treatment during pregnancy will have used buprenorphine doses which are much higher than those requested for use with Belbuca. That said, comparatively high doses of buprenorphine used to treat opioid dependent pregnant women demonstrated that the risk of adverse outcomes is low. Animal data on use of buprenorphine during organogenesis did not demonstrate an increase in congenital malformations. Neither high prenatal buprenorphine exposures for opioid dependence treatment or animal studies demonstrate a high risk of teratogenesis from buprenorphine.

DPMH recommendations for Belbuca Lactation labeling were initially based upon the published studies and toxicological database reviews of lactation in women being treated for opioid dependence. These data indicate that the risk of buprenorphine exposure to the breastfed infant is low. However, in discussion with the Division, consideration was given to their concern that the labeling for Belbuca should be consistent with that used for other ER/LA opioid drugs indicated for treatment of pain. DMPH agrees with DAAAP that breastfeeding will not be recommended for breastfeeding women who are being treated with Belbuca for pain, as is the recommendation for all ER/LA opioid drugs.

CONCLUSIONS

- No data were found on the prenatal use of buprenorphine to treat chronic pain.
- Data derived from studies of opioid dependent pregnant women treated with buprenorphine indicate that the risk of congenital malformations following such exposure is low with the caveat that the drug doses used would likely be much higher than those requested for Belbuca.
- The risk posed to a breastfeeding infant by maternal treatment with Belbuca may or may not be greater than that for non-ER/LA buprenorphine drugs. In keeping with this class of drugs, breastfeeding is not recommended.

RECOMMENDATIONS

The following are the DPMH Maternal Health Team recommendations for the proposed Belbuca labeling.

BELBUCA™ (buprenorphine hydrochloride) buccal film, CIII
Initial U.S. Approval: 1981

HIGHLIGHTS OF PRESCRIBING INFORMATION

Boxed Warning

WARNING: ADDICTION, ABUSE, and MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; and NEONATAL OPIOID WITHDRAWAL SYNDROME

- **Prolonged use of BELBUCA during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant**

woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.3)

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Not recommended. (8.2)

FULL PRESCRIBING INFORMATION: CONTENTS*

5 WARNINGS AND PRECAUTIONS

5.3 Neonatal Opioid Withdrawal Syndrome

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

17 PATIENT COUNSELING INFORMATION

FULL PRESCRIBING INFORMATION

WARNING:

ADDICTION, ABUSE, and MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; and NEONATAL OPIOID WITHDRAWAL SYNDROME

Neonatal Opioid Withdrawal Syndrome

Prolonged use of BELBUCA during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal and ensure that appropriate treatment will be available [see Warnings and Precautions (5.3)].

5 WARNINGS AND PRECAUTIONS

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of BELBUCA during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, failure to gain weight; the onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the

specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn [*see Use in Specific Populations (8.1)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of BELBUCA buccal film or buprenorphine in pregnant women. Limited published data on use of buprenorphine, the active ingredient in BELBUCA, in pregnancy have not reported an increased risk of major malformations. In animal reproduction studies embryofetal death was observed in both rats and rabbits administered buprenorphine during the period of organogenesis via the oral route of administration at doses approximately 53 to 11 times the maximum recommended human dose (MRHD), respectively. In pre- and postnatal development studies in rats, dystocia was observed after treatment with buprenorphine via the IM route of administration at a dose approximately 27 times the MRHD, and increased neonatal death was observed after treatment via the oral, IM, and SC routes of administration at doses approximately 4, 3, and 0.5 times the MRHD, respectively. No teratogenic effects were observed in rats treated with buprenorphine via the oral, IM, and IV routes of administration during organogenesis at doses approximately 853, 27, and 4 times the MRHD, respectively, or in rabbits treated with buprenorphine via the oral, SC, and IV routes of administration at doses approximately 267, 53, and 9 times the MRHD, respectively. However, in a few studies, some events such as acephalus, omphalocele, and skeletal abnormalities were observed but these findings were not clearly treatment-related [*see Data*].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, including poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly [*see Warnings and Precautions (5.3)*].

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psychophysiological effects in neonates. An opioid antagonist such as naloxone must be available for reversal of opioid induced respiratory depression in the neonate. BELBUCA is not recommended for use in women immediately prior to labor, when shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including BELBUCA, can prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However, this effect is not

consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor.

Data

Animal Data

Buprenorphine administration during organogenesis was not teratogenic in rats or rabbits after intramuscular (IM) or subcutaneous (SC) doses up to 5 mg/kg/day (estimated exposure was approximately 27 and ^{(b) (4)} times, respectively, the maximum recommended human dose (MRHD) for buccal BELBUCA of 1.8 mg on a mg/m² basis), after IV doses up to 0.8 mg/kg/day (estimated exposure was approximately 4 and 9 times, respectively, the MRHD), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 853 times the MRHD) and 25 mg/kg/day in rabbits (estimated exposure was approximately 267 times the MRHD). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration of 1 mg/kg/day and up (estimated exposure was approximately 5 times the MRHD), but were not observed at oral doses up to 160 mg/kg/day. Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day (estimated exposure was approximately 53 times the MRHD) or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately 11 times the MRHD) were not statistically significant.

In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater (estimated exposure was approximately 11 times the MRHD) and post-implantation losses that were statistically significant at IV doses of 0.2 mg/kg/day or greater (estimated exposure was approximately 2 times the MRHD).

Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine 5 mg/kg/day (approximately 27 times the MRHD). Fertility, peri- and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 4 times the MRHD), after IM doses of 0.5 mg/kg/day and up (approximately 3 times the MRHD), and after SC doses of 0.1 mg/kg/day and up (approximately 0.5 times the MRHD). Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 427 times the MRHD).

8.2 Lactation

Risk Summary

Based on two studies in 13 lactating women being treated with buprenorphine for opioid dependence and their breastfed infants buprenorphine and its metabolite norbuprenorphine are present in low levels in human milk and infant urine and available data have not shown adverse reactions in breastfed infants [see Data]. There are no data on the effects of BELBUCA on milk production. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with BELBUCA.

Clinical Considerations

Infants exposed to BELBUCA through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

Data

Based on limited data from a study of 6 lactating women being treated for opioid dependence who were taking a median oral dose of buprenorphine of 0.29 mg/kg/day 5-8 days after delivery, breast milk contained a median infant dose of 0.42 mcg/kg/day of buprenorphine and 0.33 mcg/kg/day of norbuprenorphine, which are equal to 0.2% and 0.12% of the maternal weight-adjusted dose. The median concentrations of buprenorphine and norbuprenorphine in infant urine were 1.0 nmol/L and 2.3 nmol/L, respectively.

Based on limited data from a study of 7 lactating women who were taking a median oral dose of buprenorphine of 7 mg/day an average of 1.12 months after delivery, the mean milk concentrations of buprenorphine and norbuprenorphine were 3.65 mcg/L and 1.94 mcg/L respectively. Based on the limited data from this study, and assuming milk consumption of 150 mL/kg/day, an exclusively breastfed infant would receive an estimated mean of 0.55 mcg/kg/day of buprenorphine and 0.29 mcg/kg/day of norbuprenorphine, which are 0.38% and 0.18% of the maternal weight-adjusted dose.

No adverse reactions were observed in the infants in these two studies.

17 PATIENT COUNSELING INFORMATION

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of BELBUCA during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [see *Warnings and Precautions* (5.3)].



Lactation

Advise patients that breastfeeding is not recommended during treatment with BELBUCA [see *Use in Specific Populations* (8.2)].

Medication Guide

Tell your healthcare provider if you are:

- pregnant or planning to become pregnant. Prolonged use of BELBUCA during pregnancy can cause (b) (4) withdrawal symptoms in your newborn baby if not recognized and treated.

- breastfeeding. Not recommended; [REDACTED] (b) (4)
[REDACTED]

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

/s/

CAROL H KASTEN
09/24/2015

TAMARA N JOHNSON
09/25/2015

LYNNE P YAO
09/29/2015

505(b)(2) ASSESSMENT

Application Information		
NDA # 207932	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Belbuca Established/Proper Name: buprenorphine buccal film Dosage Form: buccal film Strengths: 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, 900 mcg		
Applicant: Endo Pharmaceuticals, Inc.		
Date of Receipt: December 23, 2014		
PDUFA Goal Date: October 23, 2015	Action Goal Date (if different):	
RPM: Spiros Nicols		
Proposed Indication(s): Management of (b) (4) severe (b) (4) pain (b) (4)		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product OR is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 018401 Buprenex	FDA's previous finding of safety and effectiveness (e.g., clinical or nonclinical or both)
NDA 020732 Subutex	

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

Two BA studies (BUP-115 and BUP-117) were conducted comparing Belbuca with Buprenex injection over multiple dose ranges.

BUP-118 was a single-dose BA study comparing Belbuca doses of 900 mcg with 8 mg sublingual buprenorphine tablets (Roxane generic of Subutex product.)

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES NO
If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO
*If "NO," proceed to question #5.
If "YES", list the listed drug(s) identified by name and answer question #4(c).*

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

YES NO

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Buprenex	NDA 018401	Y
Subutex	NDA 020732	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing: Subutex

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a change in dosage form from IV to buccal and change in dose range and regimen (Buprenex) and change in dosage form from sublingual to buccal, change in dose range, and change in indication from opioid dependence to pain (Subutex) .

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.
If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"
If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): Butrans (NDA 21306) and Buprenex (NDA 18401) are approved for pain indications. Buprenex is referenced as a listed drug and Butrans is not. There are generics to Buprenex and there are no generics to Butrans. Subutex and its generics are approved for the treatment of opioid dependence, however, their dosing is higher than that for Belbuca. Note that the other buprenorphine products are combined with naloxone.

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

SPIROS NICOLS
09/14/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: September 4, 2015

Requesting Office or Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Application Type and Number: NDA 207932

Product Name and Strength: Belbuca (buprenorphine hydrochloride) buccal film, 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, 900 mcg

Submission Date: September 3, 2015

Applicant/Sponsor Name: Endo Pharmaceuticals, Inc.

OSE RCM #: 2014-2627

DMEPA Primary Reviewer: Millie Shah, PharmD, BCPS

DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised container label (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling reviews.^{1,2,3}

¹ Shah M. Label and Labeling Review for Belbuca (buprenorphine hydrochloride) buccal film (NDA 207932). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 APR 24. 18 p. OSE RCM No.: 2014-2627.

² Shah M. Label and Labeling Memo for Belbuca (buprenorphine hydrochloride) buccal film (NDA 207932). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 AUG 06. 10 p. OSE RCM No.: 2014-2627.

³ Shah M. Label and Labeling Memo for Belbuca (buprenorphine hydrochloride) buccal film (NDA 207932). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and

2 CONCLUSIONS

The revised container label for the 600 mcg strength is acceptable from a medication error perspective.

APPENDIX A. LABEL SUBMITTED ON SEPTEMBER 1, 2015

Belbuca (buprenorphine hydrochloride) container label, 600 mcg



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/s/

MILLIE C BRAHMBHATT
09/04/2015

BRENDA V BORDERS-HEMPHILL
09/04/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: September 1, 2015

Requesting Office or Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Application Type and Number: NDA 207932

Product Name and Strength: Belbuca (buprenorphine hydrochloride) buccal film, 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, 900 mcg

Submission Date: August 26, 2015

Applicant/Sponsor Name: Endo Pharmaceuticals, Inc.

OSE RCM #: 2014-2627

DMEPA Primary Reviewer: Millie Shah, PharmD, BCPS

DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised container labels (Appendix A) to determine if it is acceptable from a

¹ Shah M. Label and Labeling Review for Belbuca (buprenorphine hydrochloride) buccal film (NDA 207932). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 APR 24. 18 p. OSE RCM No.: 2014-2627.

² Shah M. Label and Labeling Memo for Belbuca (buprenorphine hydrochloride) buccal film (NDA 207932). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 AUG 06. 10 p. OSE RCM No.: 2014-2627.

³ Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling reviews.^{1,2}

2 CONCLUSIONS

The revised container labels for the following strengths are acceptable from a medication error perspective: 75 mcg, 150 mcg, 300 mcg, 450 mcg, 750 mcg, and 900 mcg. The revised container label for the 600 mcg strength is unacceptable from a medication error perspective. We recommend the Sponsor revise the presentation of the expiration date on the 600 mcg container label from (b) (4) to “MMYYYY” to mitigate the risk for confusion.³

APPENDIX A. LABELS SUBMITTED ON AUGUST 25, 2015

Belbuca (buprenorphine hydrochloride) container label, 75 mcg

(b) (4)



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/s/

MILLIE C BRAHMBHATT
09/01/2015

BRENDA V BORDERS-HEMPHILL
09/01/2015



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: August 27, 2015

To: Sharon Hertz, M.D., Director
Division of Analgesics, Anesthesia, and Addiction

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Jovita Randall-Thompson, Ph.D., Pharmacologist
Controlled Substance Staff

Alan Trachtenberg, M.D., MPH, Medical Officer
Controlled Substance Staff

Subject: Belbuca Buccal Film - NDA 207932
Generic Name (Trade Name): Buprenorphine Hydrochloride Buccal Film
Dosages: 75 µg, 150 µg, 300 µg, 450 µg, 600 µg, 750 µg, and 900 µg of buprenorphine twice a day
Formulations: 75 µg, 150 µg, 300 µg, 450 µg, 600 µg, 750 µg, and 900 µg buprenorphine films
Route: buccal
NDA/IND Number(s): IND 072428
Indication(s): For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment
Sponsor: Endo Pharmaceuticals, Inc.
PDUFA Goal Date: October 23, 2015

Materials Reviewed:

- NDA 207932/ Module 1.11.4 Abuse Liability Assessment, dated December 9, 2014
- NDA 207932/ Module 3.2.P.1 Description and Composition, dated November 25, 2014
- NDA 207932/ Module 1.14.1.3 Labeling/ Medication Guide
- Phase 1 Study Reports: BUP-110, BUP-115, BUP-116, BUP-117, BUP-118, and EN3409-120
- Phase 2 Study Reports: BUP-201, and EN3409-204
- Phase 3 Study Reports: BUP-301, EN3409-307, EN3409-308, BUP-305, and EN3409-309

Table of Contents

MEMORANDUM 1

Materials Reviewed: 1

I. Summary 2

1. Background 2

2. Conclusions 3

3. Recommendations 3

II. Discussion 3

1. Chemistry 4

1.1 Substance information 4

2. Absorption, Distribution, Metabolism, Elimination (ADME) 4

3. Adverse event profile through all phases of development 5

4. Safety profile 7

4.1 Evidence of abuse, misuse and diversion in clinical trials 7

I. Summary

1. Background

This memorandum responds to a consult dated January 6, 2015, from the Division of Analgesia, Anesthesia, and Addiction Products (DAAAP). The consult pertains to a new drug application (NDA), NDA 207932, for the buprenorphine (BUP) product Belbuca, a BUP hydrochloride buccal film submitted by Endo Pharmaceuticals, Inc. DAAAP requested that CSS review the NDA from a controlled substance/abuse potential perspective.

Endo is seeking approval of Belbuca for the management of pain severe enough to require daily, around-the-clock (ATC), long-term opioid treatment and for which alternative treatment options are inadequate (b) (4). Belbuca buccal film is a long acting product taken twice a day. The long acting effects of Belbuca are due to BUP long mean elimination half-life (oral): a range of 16 -72 hours and an average of 37 hours. The BUP Buccal Film has the same two layer film delivery technology, BioErodible Mucoadhesive (BEMA), used in the approved product Bunavail® (BUP and naloxone, NDA 205637/Endo Pharmaceuticals, approved 05/06/2014) indicated for treatment of opioid dependence.

Endo submitted the supplement under section 505(b)(2) on December 23, 2014, referencing Buprenex® (NDA 018401/Norwich-Eaton Pharma (previously Reckitt Benckiser), approved 12/ 29/1981, EQ 0.3 mg base/ml), an injectable (IV or IM) that has the same indication as the proposed BUP buccal film. Though discontinued, Subutex® (NDA 020732, approved 10/08/02, EQ 2 mg, 4 mg/base) is also referenced, as several generics are still marketed. The proposed BUP buccal film also has an indication that is the same as another marketed buprenorphine single ingredient product, BuTrans® (NDA 021306/ Purdue Pharma L.P., approved 05/30/2010, 7.5, 10, 15, and 20 mcg/hour), a transdermal patch that provides analgesia and is worn for 7 days. BuTrans® is subject to the Extended-Release and Long-Acting Opioid Analgesics Shared Risk Evaluation and Mitigation

Strategy (REMS) program (long-acting due to buprenorphine's pharmacokinetics and extended-release due to modified-release properties).

In the current application, study findings for the efficacy/safety of Belbuca film taken buccally is supported by 9 Phase 1 studies, 2 Phase 2 studies and 5 Phase 3 studies evaluating Belbuca over 60 to 1200 µg taken buccally.

The primary bases of our conclusions and recommendation are the Endo's abuse liability assessment in NDA 207932, which includes an adverse event (AE) evaluation of all Phase 3 studies and an assessment of the abuse-related treatment emergent adverse event findings collected in Phase 1 for the final marketed formulation.

2. Conclusions

1. Belbuca buccal film is a buprenorphine formulation indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment, submitted under a 505(b)(2) NDA application.
2. Buprenorphine is an opioid (partial) agonist and is listed by the Drug Enforcement Administration (DEA) as a Schedule III (CIII) drug under the Controlled Substances Act (CSA), Therefore, due to the presence of buprenorphine, Belbuca buccal film is a CIII drug.
3. From an abuse perspective, there were no measurable differences in the abuse-related AE profiles of Belbuca buccal film in comparison to other marketed buprenorphine products (Buprenex[®], Subutex[®]).

3. Recommendations

Based on our findings as captured in the Conclusions section, we recommend the following:

1. The language proposed for the product label on the risks of abuse and dependence, including Section 9.0 and the black box warning, should remain the same as currently written in the existing label of BuTrans[®] and other buprenorphine products indicated for pain.

II. Discussion

Belbuca buccal film that contains buprenorphine (BUP), a partial μ -agonist, (blocks and activates) and a κ -antagonist (blocks activity) (for review, see Lutfy & Cowan, 2004), which has little or no agonist properties at κ -receptors (Zhu et al., 1997; Toll et al., 1998) and no agonist actions at the δ -receptors (Toll et al., 1998).

Belbuca is a Schedule III narcotic as other currently single and combination products containing BUP base or its salt. It is indicated for opioid dependence. It has the same film delivery technology, BioErodible Mucoadhesive (BEMA), used in the approved product Bunavail[®] (buprenorphine and naloxone, NDA 205637, approved 05/06/2014) indicated for opioid dependence.

Bunavail[®] is a two layer film containing BUP and naloxone of which BUP is present in the mucoadhesive layer (ML) and naloxone is present in the inactive layer (IL). Both Belbuca and Bunavail[®] films are administered by placing the ML against the inside of the cheek where BUP is absorbed through the buccal mucosa. For the BUP

Buccal Film, there is no drug in the IL thus no substance is released from the IL, whereas for Bunavail[®] naloxone is released from the IL and is swallowed. Although not claimed, naloxone, an opioid antagonist, blocks the mu agonist effects of BUP but is only active if Bunavail[®] is dissolved in a solution in order to extract buprenorphine for parenteral or intranasal administration. This is a typical method of manipulation and these are the main routes of abuse of buprenorphine by abusers. However, according to a CMC review (see DARRTS, NDA 205637, Shaw, Arthur B., review dated May 6, 2014; also see DARRTS, NDA 205637, Calderon, Silvia N., review dated 05/13/2014) when the Bunavail[®] BEMA film is dissolved in (b) (4), its BUP content can be extracted selectively without naloxone (b) (4). The solution potentially can be used as an injectable solution. When taken at high doses, BUP can precipitate withdrawal in opioid dependent users and has a ceiling effect on respiratory depression that limits the incidence of overdose (except when used with alcohol or another psychoactive drug, benzodiazepines or opioids) associated with its use compared to a full opioid agonist (e.g., morphine).

1. Chemistry

The active pharmaceutical ingredient of Belbuca, buprenorphine HCl (BUP), chemical name is (2S)-2-[17-Cyclopropylmethyl-4,5 α -epoxy-3-hydroxy-6-methoxy-6 α ,14-ethano14 α -morphinan-7 α -yl]-3,3-dimethylbutan-2-ol hydrochloride (molecular formula C₂₉ H₄₁ NO₄ • HCl; molecular weight is 504.10

1.1 Substance information

The strength of the film is dependent on the formulation and the size. There are 2 formulations used to manufacture Belbuca. (b) (4) 75 μ g and 150 μ g strengths and the size of each film is 1.215 and 2.431 cm² respectively. (b) (4) 300 μ g, 450 μ g, 600 μ g, 750 μ g and 900 μ g strengths, and the size of each film is 0.934, 1.400, 1.867, 2.334 and 2.801 cm². (b) (4) All Belbuca films are rectangular in shape with rounded corners.

The total BUP content varies by the dose of the film (dose/total mg), 75 μ g (b) (4) mg, 150 μ g (b) (4) mg, 300 μ g (b) (4) mg, 450 μ g (b) (4) mg, 600 μ g (b) (4) mg, 750 μ g (b) (4) mg, and 900 μ g (b) (4) mg (Endo 3.2.P.1 Description and Composition, dated 09/27/2013, Table 2: Composition of BEMA Films). The strength of each film is dependent on the BUP concentration in the formulation and the surface area of the film.

Treatment is initiated in opioid naïve patients with a 75 μ g film once daily or, if tolerated, every 12 hours for at least 4 days then dose is increased 150 μ g every 12 hours and titration to a dose that provides adequate analgesia while minimizing adverse reactions. The maximum dose is 450 μ g every 12 hours.

2. Absorption, Distribution, Metabolism, Elimination (ADME)

Buprenorphine displays poor oral bioavailability. However, its bioavailability improves when it is administered sublingually. The same holds for when taken buccally. The absolute bioavailability of Belbuca ranged from 46 to 65%.

Plasma concentrations (C_{max}) and drug exposure (AUC) of buprenorphine increase linearly, though not in direct dose proportionality, with increasing sublingual dose over a range of 4 - 16 mg. Similarly, as stated by Sponsor for Belbuca, systemic plasma levels of buprenorphine increased in a linear manner (C_{max} and AUC) over the single dose range of 75 to 1200 mcg (see proposed label). The mean elimination half-life of sublingually administered buprenorphine is 37 hours (Clinical Pharmacology Online). Based on multiple dose studies performed with Belbuca, the mean plasma elimination half-life of buprenorphine was 27.6 \pm 11.2 hours (comparable also to BuTrans^{®1}).

3. Adverse event profile through all phases of development

Abuse-related TEAEs were reported in Phase 1 studies BUP-115, BUP-116, BUP-117, BUP-118, and EN3409-120 and Phase 3 studies BUP-301, EN3409-307, EN3409-308 BUP-305 and EN3409-309. There were two Phase 2 studies, however Phase 2 AEs were not assessed because the final marketed formulations (b) (4) were not evaluated in Phase 2 Study BUP-201 and due to the study design of Phase 2 Study EN34090-204, which employs a switch cross-over design, for opioid-dependent subjects treated for pain are switched from oxycodone to Belbuca (the BEMA BUP Buccal film).

Specifically, the review assesses those AEs reported with the final dosage formulations, including (b) (4) at various strengths including final to-be-marketed strengths (75, 150, 300, 450, 600, 750 and 900 µg) in subjects that were opioid naive or opioid experienced but not opioid-dependent at the start of a study.

Only Phase 1 Studies BUP-115 and BUP-117 included a Buprenex® treatment arm. For those abuse-related TEAEs reported in Phase 1 Study Reports, among the system organ categories dizziness, euphoric mood, sedation and disturbance in attention are mentioned. Belbuca's (BEMA BUP Buccal) abuse-related AE counts are provided below.

Other AEs reported that are often accompanied with abuse but are not typically considered euphoric-like, included nausea, vomiting and fatigue of which are not listed below due to low counts or lack of clinical meaningfulness as it relates to abuse among the sample population that was assessed.

Each study included a naltrexone HCl 25 or 50 mg, oral administration approximately 12 hours prior to, 30 minutes prior to, 12 hours after, and 24 hours after buprenorphine administration during each treatment period.

1) Study BUP-115: Treatments included BEMA BUP Buccal (b) (4) at 0.5, (also assessed, 0.2 mg/ (b) (4), 1.5 mg/ (b) (4); 0.5 mg Buprenex IV, and 50 mg naltrexone), N=40. No abuse-related AEs reported for 0.5 mg/ (b) (4) and no placebo assessed.

2) Study BUP-116: Treatments included BEMA BUP Buccal (b) (4) at 60, 120, 180, and 240 µg/1 dose level per 72-hour study period, and 25 mg naltrexone, N=10. For BEMA BUP Buccal, a somnolence count of N=1 (10%) at 60 µg, and an euphoric mood count of N=1 (10%) at 120 µg were reported; and no placebo assessed

3) Study BUP-117: Treatments included BEMA BUP Buccal (b) (4) at 75 and 300 µg and (b) (4) at 300 and 1200 µg and 300 µg Buprenex IV and 50 mg naltrexone, N=21 – 23. For BEMA BUP Buccal dizziness counts of N=1 (4.5%) at 300 µg (b) (4) and N=1 (4.3%) at 1200 µg (b) (4), a somnolence count of N=1 (4.8%) at 300 µg (b) (4) and N=1 (4.3%) at 1200 µg (b) (4), and a disturbance in attention of N=1 (4.5%) at 75 µg (b) (4) were reported; and no placebo assessed.

4) Study BUP-118: Treatments included BEMA BUP Buccal (b) (4) at 900 µg with or without carbonated liquids at room temperature and 8 mg BUP sublingual tablet without liquids and 50 mg naltrexone, N=26-29. For BEMA BUP Buccal dizziness counts of N=1 (3.4%) with no liquids, 1 (3.3%) with decaf cola and 1 (3.6%) with sodium bicarbonate mixed with water and a somnolence count of N=1 (3.6%) with sodium bicarbonate mixed with water were reported; no placebo assessed.

¹ After removal of the system (BuTrans®), mean buprenorphine concentrations decreased by 50% within 10–24 hours. The terminal half-life is approximately 26 hours (BuTrans® Package Insert. Stamford, CT: Purdue Pharma L.P.; 2014 Jun.).

5) Study EN3409-120: BEMA BUP Buccal (b) (4) with or without liquids hot or cold and 50 mg naltrexone, N=31-32, somnolence counts of 2 (6.3%) without liquid, 1 (3.2%) when taken with hot, cold water or room temperature water (separately) were reported; no placebo assessed.

Phase 3 Studies BUP-301, EN3409-307, EN3409-308 included an Open-label Titration Period and Double-blind Treatment Period (placebo-controlled), while Phase 3 Studies BUP-305 and EN3409-309 consisted of a Titration Period and a Long-term Treatment Period (uncontrolled). For those abuse-related TEAEs reported in Phase 3 Study Reports, among the system organ categories for all study experimental periods, dizziness, euphoric mood, sedation, feeling drunk, libido increase and disturbance in attention are mentioned. BEMA BUP Buccal's abuse-related AE counts are provided below.

Other AEs reported that are often accompanied with abuse but are not typically considered euphoric-like included nausea, vomiting, disorientation, restlessness, irritability, confusional state, lethargy, cold sweat, feeling jittery, listless, anxiety, feeling abnormal, drug withdrawal syndrome and fatigue of which are not listed below due to low counts.

Each study included a naltrexone HCl 25 or 50 mg, oral administration approximately 12 hours prior to, 30 minutes prior to, 12 hours after, and 24 hours after buprenorphine administration during each treatment period.

1) Study BUP-301: Treatments included BEMA BUP Buccal (b) (4) 60, 120, 180, and 240 µg; each dosed every 12 hours only if patients had been taking 2 doses per day for at least 3 days prior to the dose increase, N=330. For BEMA BUP Buccal, open label titration period (N=330), dizziness counts of N=30 (9.1%), somnolence counts of N=12 (3.6%) for nervous system disorders and somnolence counts of N=9 (2.7%) for psychiatric disorders, sedation counts of N=2 (0.6%), euphoric mood counts of N=3 (0.9%), libido increase counts of N=3 (0.9%), and feeling drunk counts of N=3 (0.9%) were reported. For the placebo control double blind period (N=73), dizziness counts of N=4 (3.4%), somnolence count of N=1 (0.9%) for psychiatric disorders and euphoric mood count of N=1 (0.9%) were reported.

2) Study EN3409-307: Treatments included BEMA BUP Buccal (b) (4) 150, 130, 450, 600, 750 and 900 µg; each dosed every 12 hours only if patients had been taking 2 doses per day for at least 3 days prior to the dose increase, N=810. For BEMA BUP Buccal, open label titration period (N=810), dizziness counts of N=42 (5.2%), somnolence counts of N=41 (5.1%) for nervous system disorders, sedation counts of N=3 (0.4%), euphoric mood counts of N=1 (0.1%), and feeling drunk counts of N=2 (0.2%) were reported. For the placebo control double blind period (N=254) dizziness counts of N=2 (0.8%) and somnolence count of N=1 (0.9%) were reported.

3) Study EN3409-308: Treatments included BEMA BUP Buccal (b) (4) at 75 and 300 µg and (b) (4) at 300 and 1200 µg and 300 µg Buprenex IV and 50 mg naltrexone, N=21 – 23. For BEMA BUP Buccal dizziness counts of N=1 (4.5%) at 300 µg (b) (4) and N=1 (4.3%) at 1200 µg (b) (4) a somnolence count of N=1 (4.8%) at 300 µg (b) (4) and N=1 (4.3%) at 1200 µg (b) (4), and a disturbance in attention of N=1 (4.5%) at 75 µg (b) (4) were reported; and no placebo assessed.

4) Study BUP-305: Treatments included BEMA BUP Buccal (b) (4) at 900 µg with or without carbonated liquids at room temperature and 8 mg BUP sublingual tablet without liquids and 50 mg naltrexone, N=26-29. For BEMA BUP Buccal dizziness counts of N=1 (3.4%) with no liquids, 1 (3.3%) with decaf cola and 1 (3.6%)

with sodium bicarbonate mixed with water and a somnolence count of N=1 (3.6%) with sodium bicarbonate mixed with water were reported; no placebo assessed.

5) Study EN3409-309: BEMA BUP Buccal ^{(b) (4)} with or without liquids hot or cold and 50 mg naltrexone, N=31-32, a dizziness count of N=0 (0%), and somnolence counts of 2 (6.3%) without liquid, 1 (3.2%) when taken with hot, cold water or room temperature water (separately) were reported; no placebo assessed.

No other abuse-related AEs were reported. The majority of the abuse-related AEs reported with BEMA BUP Buccal were below 5%. In addition, the counts of abuse-related AEs reported with BEMA BUP Buccal did not differ from the AE counts reported with naltrexone, BUP sublingual tablet and Buprenix.

4. Safety profile

As reported by the Sponsor, there were two cases of non-fatal overdose (subject EN3409-308-1027-8014, attempted suicide with mixed use of alprazolam and diazepam, cerofolin and alcohol; subject EN3409-308-1025-806, subject took one extra dose of study drug (see 1.11.4 Abuse Liability Assessment, pg. 15). One patient receiving BEMA BUP Buccal 60 µg twice daily, died from cardiac arrhythmia due to diabetic complication (Study BUP-305, subject BUP-305-008-016, see 1.11.4 Abuse Liability Assessment, pg. 22). During Phase 3 testing, there were no reports of tolerance, however the Sponsor states that drug withdrawal syndrome was reported 60 out of 2127 subjects.

No unintended pediatric exposure or homicidal incidences were reported in any of the Phase 1, 2 and 3 clinical studies conducted under the current submission.

4.1 Evidence of abuse, misuse and diversion in clinical trials

For Phase 1 and 2 studies, the administration of Belbuca was carried out by a nurse. The nurse placed each soluble film in the subject's mouth and recorded the number of films and tablets applied; thus at no time were subjects given BEMA BUP Buccal to administer on their own.

As for Phase 3 studies, BUP-301, EN3409-307, EN3409-308, BUP-305 and EN3409-309 subjects were instructed to return all unused and partially used study medication and test articles at all protocol-specified visits for drug inventory and assessment of subject compliance. An accurate and current accounting of the dispensing and return of study drug(s) for each subject was maintained on an ongoing basis by a member of the study site staff in a drug accountability log and was verified by the sponsor's study monitor. There was no incidence of misuse and diversion reported.

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/s/

JOVITA F RANDALL-THOMPSON
08/27/2015

MICHAEL KLEIN
08/27/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: August 6, 2015

Requesting Office or Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Application Type and Number: NDA 207932

Product Name and Strength: Belbuca (buprenorphine hydrochloride) buccal film, 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, 900 mcg

Submission Date: July 27, 2015

Applicant/Sponsor Name: Endo Pharmaceuticals, Inc.

OSE RCM #: 2014-2627

DMEPA Primary Reviewer: Millie Shah, PharmD, BCPS

DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised container labels and carton labeling (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

¹ Shah M. Label and Labeling Review for Belbuca (buprenorphine hydrochloride) buccal film (NDA 207932). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 APR 24. 18 p. OSE RCM No.: 2014-2627.

2 CONCLUSIONS

The revised carton labeling is acceptable from a medication error perspective. The revised container labels are unacceptable from a medication error perspective. We recommend the Sponsor revise the presentation of the expiration date on the container labels from “MMMYYY” to “MMMYYYY” to mitigate the risk for confusion.²

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

² Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

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MILLIE C BRAHMBHATT
08/06/2015

BRENDA V BORDERS-HEMPHILL
08/06/2015

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: August 6, 2015

TO: Spiros Nicols, Pharm.D., M.B.A., Regulatory Project Manager
Pamela Horn, M.D., Medical Officer
Joshua Lloyd, M.D., Team Leader
Division of Analgesia, Anesthesia, and Addiction Products

FROM: John Lee M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H., Team Leader
Kassa Ayalew, M.D., M.P.H., Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

APPLICATIONS: NDA 207932

APPLICANT: Endo Pharmaceuticals, Inc.

DRUG: Buprenorphine (Belbuca®)

NME: No

INDICATION: For the management of pain severe enough to require daily, around-the-clock, long-term treatment for which alternative treatment options are inadequate

REVIEW CLASSIFICATION: Standard

DARRTS CONSULTATION DATE: February 24, 2015

INSPECTION SUMMARY GOAL DATE: August 23, 2015

REGULATORY ACTION GOAL DATE: October 23, 2015

PDUFA DUE DATE: October 23, 2015

I. BACKGROUND

Endo Pharmaceuticals Inc. (**Endo**) submitted this 505(b)(2) NDA 207932 for buprenorphine (proposed trade name Belbuca[®]), a buccal film formulation of a long-acting opioid. The buccal formulation relies on the dissolution of flexible polymeric film to systemically deliver buprenorphine through buccal mucosal absorption, by-passing the gastrointestinal tract and any first-pass metabolic drug elimination. Endo's proposed indication for use is "management of pain severe enough to require daily, around-the-clock, long-term treatment for which alternative treatment options are inadequate" in opioid-experienced or opioid-naive patients. In support of this NDA review, Studies EN3409-307 and EN3409-308 (both conducted under IND 072428) were identified for audit at good clinical practice (**GCP**) inspections of two clinical investigator (**CI**) sites (one site per study). The two studies are described briefly below, with emphasis on study features important to inspection.

Study EN3409-307

A Phase 3, Double-blind, Placebo-Controlled, Multicenter, Randomized Withdrawal Study to Evaluate the Analgesic Efficacy, Safety, and Tolerability of BEMA[®] Buprenorphine in Opioid-Experienced Subjects with Moderate to Severe Chronic Low Back Pain Requiring Around-the-Clock Opioid Analgesia for an Extended Period of Time

This double-blind, placebo-controlled, randomized withdrawal study was conducted over 21 months (September 2012 to June 2014) in 810 subjects enrolled at 66 United States (**US**) clinical investigator (**CI**) sites. After stabilization during open-label treatment, 510 treatment responders were randomized, of whom 491 were deemed by the sponsor to be evaluable according to the criteria for the primary intention-to-treat (**ITT**) analysis.

- The primary study objective was to determine the analgesic efficacy of buprenorphine buccal film applied every 12 hours (**Q12h**) in opioid-experienced subjects with moderate to severe chronic low back pain (**CLBP**) requiring continuous around-the-clock (**ATC**) opioid analgesia for an extended period of time.
- The study consisted of five periods: (1) screening, (2) analgesic taper, (3) enrollment into open-label dose titration, (4) randomization and blinded treatment withdrawal, and (5) safety follow up.

Subject Selection

- Opioid-experienced men or women (age ≥ 18 years) with moderate to severe CLBP requiring continuous ATC opioid analgesia for an extended period of time
- Moderate to severe CLBP (primary source of chronic pain) for over six months, treated for over four weeks using an ATC opioid analgesic at a stable daily maintenance dose equivalent to ≥ 30 and ≤ 160 mg of morphine sulfate
- CLBP qualified according to Quebec Task Force (**QTF**) Classification of Spinal Disorders: (1) non-neuropathic (class 1 and 2); (2) neuropathic (class 3, 4, 5, and 6); or (3) symptomatic for more than 6 months after low back pain surgery (class 9)
- Additional as required (**PRN**) analgesic rescue medications permitted in addition to ATC morphine sulfate equivalent (**MSE**), not to exceed 160 mg MSE per day; average daily pain intensity score ≥ 11 over last 14 days of screening period
- Successful analgesic taper during which the dose of any prior opioid analgesic was reduced to below 30 mg MSE, with discontinuation of all non-opioid analgesic and all PRN opioid analgesic medications (screening Visit 2)
- Pain control during analgesic taper, assessed using 11-point numerical rating scale (**NRS**) for pain intensity, mean daily NRS score over last seven days: well controlled if < 5 , poorly controlled if ≥ 5

- Subjects with well controlled pain: CLBP confirmed to be of sufficient (study-eligible) severity by at least three consecutive average daily NRS score ≥ 5 without rescue medication use
- Once confirmed, hydrocodone/acetaminophen (**HC/APAP**) was permitted as rescue for the rest of analgesic taper (up to four doses per day, 5 mg/325 mg Q6h PRN)

Treatment Groups and Regimen

- Open-label titration (eight weeks): buprenorphine buccal film Q12h (150, 300, 450, 600, 750, or 900 μg buprenorphine per film)
 - Initial dose calculated using MSE-buprenorphine dose conversion chart, then dose-titration for optimal treatment response satisfactory for analgesia and tolerability, preferably without need for analgesic rescue (no more than one dose of HC/APAP per day)
 - Completion of dose adjustment by Week 6 to qualify for randomization at Week 8, subject concurrence with continued treatment at same dose during 12 weeks of double-blind treatment
- Double-blinded treatment withdrawal (12 weeks): baseline evaluation and 1:1 randomization to continued buprenorphine or placebo, buccal film Q12h
 - Analgesic rescue using HC/APAP 5 mg/325 mg Q6h PRN, up to two doses per day during first two weeks, no more than one dose per day after first two weeks
 - Subjects experiencing opioid withdrawal as determined by Clinical Opiate Withdrawal Scale (**COWS**) score ≥ 13 were discontinued from the study.
 - Subjective Opiate Withdrawal Scale (**SOWS**) assessment at or between Visits 19 and 20
- Safety follow-up: Discontinuation of all study medication and follow-up safety evaluation, with option to either enroll in the open-label safety Study EN3409-309 or continued treatment using an analgesic regimen at CI discretion
- End of study (**EOS**) Visit 27 and phone follow up two weeks later to collect safety information including adverse events (**AEs**) and concomitant medication use

Major Endpoints

- Primary efficacy endpoint: Change from baseline to Week 12 (blinded treatment) in mean daily NRS pain intensity score
- Secondary efficacy endpoints:
 - Proportion of responders from start of open-label titration to week 12 of blinded treatment
 - Opioid rescue medication use over the 12-week double-blind treatment phase
 - Time to “optimal” dose of open-label study medication in the open-label titration phase
 - Time to treatment failure in the double-blind treatment phase
 - Patient Global Impression of Change (**PGIC**)
 - Roland Morris Disability Questionnaire (**RMDQ**)
- Major safety endpoints:
 - Clinical AEs
 - Laboratory tests
 - Urine dipstick for drugs of abuse
 - For women, on-site urine pregnancy testing
 - Electronic Columbia-Suicide Severity Rating Scale (**eC-SSRS**)

Sponsor-Reported Outcomes

- Primary efficacy: Relative to placebo, buprenorphine treatment showed significantly ($p < 0.00001$) smaller mean change in NRS pain intensity score from baseline to week 12 of blinded treatment. Treatment difference favoring buprenorphine was observed at each week of blinded treatment.
- The results of all secondary efficacy endpoints were consistent with the primary endpoint results: relative to placebo, the proportions of subjects with clinically significant levels of pain reduction ($\geq 50\%$ or $\geq 30\%$) from baseline to Week 12 of blinded treatment were significantly greater for buprenorphine (40% vs 17% or 64% vs 31% respectively, $p < 0.0001$).
- The observed safety profile was consistent with that known for buprenorphine. The buccal film formulation was well tolerated in opioid-experienced subjects with moderate to severe CLBP.

Study EN3409-308

A Phase 3, double-blind, placebo-controlled, multicenter, randomized withdrawal study to evaluate the analgesic efficacy, safety, and tolerability of BEMA® buprenorphine in opioid-naive subjects with moderate to severe chronic low back pain requiring around-the-clock opioid analgesia for an extended period of time

This study is nearly identical in design to Study EN3409-307 (including study title), with opioid-naive subject population as the major difference. Endo claims that the efficacy and safety outcomes of this study corroborate those of Study EN3409-307.

Study EN3409-308 was conducted over 16 months (August 2012 to December 2013) in 749 subjects enrolled at 60 CI sites in the US. After open-label treatment, 461 treatment responders were randomized, of whom 420 were deemed by the sponsor to be evaluable according to the criteria for the primary ITT analysis. The primary study objective was to determine the analgesic efficacy of buprenorphine buccal film applied Q12h in opioid-naive subjects with moderate to severe CLBP requiring continuous ATC opioid analgesia for an extended period of time.

II. INSPECTIONS

In auditing Studies 307 and 308, the following two CI sites were identified for GCP inspection based on their large contribution to the primary efficacy outcome (respective study, sponsor report). No special concerns were identified for protocol violations, AEs, or CI conflicts of interest for either study.

Clinical Investigator		Study, Site, Enrollment	Inspection Outcome
1	James E. Wild, M.D. Upstate Clinical Research Associates 8201 Main Street, Suite 1 Williamsville, New York	Study 307 Site 1009 49 enrolled, 30 randomized	May 12-20, 2015 NAI
2	Bruce G. Rankin, D.O. Avail Clinical Research, LLC 860 Peachwood Drive Deland, Florida	Study 308 Site 1040 25 enrolled, 12 randomized	May 4 - 8, 2015 VAI

NAI = no action indicated (no significant violations); VAI = voluntary action indicated (minor violations)

1. James E. Wild, M.D.

a. What was inspected:

- Records review: local institutional review board (**IRB**) oversight and sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject records
- Subject records: subject screening and eligibility, informed consent, treatment compliance, and data verification
- Data verification: randomization, major efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study 307, Site 1009: 66 subjects were screened, 49 were enrolled, 30 were randomized, and 24 completed the study. Case records were reviewed for all enrolled subjects, including detailed review for 22 randomized subjects.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared adequate, including informed consent, drug accountability, AE monitoring, and reporting of AEs and protocol deviations. IRB oversight and sponsor monitoring appeared acceptable. Source records were well maintained. All audited endpoint data were verifiable among source records, case report forms (**CRFs**), and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.

2. Bruce G. Rankin, D.O.

a. What was inspected:

- Records review: IRB oversight and sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject records
- Subject records: subject screening and eligibility, informed consent, treatment compliance, and data verification
- Data verification: randomization, major efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study 308, Site 1040: 48 subjects were screened, 25 were enrolled, 12 were randomized, and nine completed the study. Case records were reviewed for all subjects, including detailed review for all enrolled subjects.

A Form FDA 483 was issued for the following observations, apparent protocol deviations (relative to Amendment 3) not reported in the NDA (as protocol deviations): (1) for Subjects 8003 and 8004, Visit 14 urine dipstick screening test for drugs of abuse and Visit 19 suicidality assessment (eC-SSRS) were not performed; (2) Subject 8022 was enrolled into open-label treatment despite pain intensity reporting rate (daily over last two weeks) of 71% ($\geq 80\%$ specified in protocol); and (3) for Subject 8042, Visit 19 urine pregnancy testing was not performed.

These (apparent deficiency) observations appear minor, isolated, and unlikely to be significant. The overall study conduct appeared adequate, as did IRB oversight and sponsor monitoring of study conduct. Study records were well maintained. All audited endpoint data were verifiable among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.

III. OVERALL ASSESSMENT AND RECOMMENDATIONS

Endo submitted this 505(b)(2) NDA 207932 for Belbuca[®], a buccal film formulation of the long-acting opioid buprenorphine. To confirm adequate adherence to GCP (as assessed at NDA review) in conducting the pivotal Studies EN3409-307 and EN3409-308, a limited sample of two CI sites were inspected, selected for large contribution to the (respective study) efficacy outcome. At the two CI sites combined, case records for all enrolled subjects were reviewed (5% of 1559 combined overall study enrollment), including detailed review for 47 subjects (3% of combined enrollment). No significant deficiencies were observed at either CI site: study conduct and data reporting appeared adequate and all audited data were verifiable among source records, CRFs, and NDA data listings. The data from the CI sites appear reliable as reported in the NDA, and more generally, the sponsor's monitoring of study conduct support adequate adherence to GCP overall for the two pivotal studies.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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/s/

JONG HOON LEE
08/06/2015

JANICE K POHLMAN
08/06/2015

KASSA AYALEW
08/06/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: July 30, 2015

To: Sharon Hertz, MD
Acting Director
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Koung Lee, RPh, MSHS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established name): BELBUCA (buprenorphine)

Dosage Form and Route: buccal film, CIII

Application Type/Number: NDA 207932

Applicant: Endo Pharmaceuticals Inc.

1 INTRODUCTION

On December 23, 2014, Endo Pharmaceuticals Inc. submitted for the Agency's review an original 505(2)(2) New Drug Application (NDA) 207932 for BELBUCA (buprenorphine) buccal film. The proposed indication is for management of (b) (4) pain severe enough to require daily, around-the-clock (ATC), long-term opioid treatment and for which alternative treatment options are inadequate in both opioid-experienced and opioid-naïve populations.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on February 20, 2015, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for BELBUCA (buprenorphine) buccal film.

2 MATERIAL REVIEWED

- Draft BELBUCA (buprenorphine) buccal film MG received on December 23, 2014, and received by DMPP and OPDP on July 24, 2015.
- Draft BELBUCA (buprenorphine) buccal film IFU received on December 23, 2014, and received by DMPP and OPDP on July 24, 2015.
- Draft BELBUCA (buprenorphine) buccal film Prescribing Information (PI) received on December 23, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 24, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
07/30/2015

KOUNG U LEE
07/30/2015

BARBARA A FULLER
07/31/2015

LASHAWN M GRIFFITHS
08/02/2015



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: June 17, 2015

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Spiros Nicols, RPM
DAAAP

Subject: QT-IRT Consult to NDA 207932

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 2/24/2015 regarding your request for estimation of the expected QT prolongation for the entire range of Belbuca (buprenorphine hydrochloride) buccal film. The QT-IRT received and reviewed the following materials:

- Your consult
- QT-IRT previous review for BEMA buprenorphine under IND 72428 (6/19/2013 and 6/30/2014)

- [REDACTED] (b) (4)

QT-IRT Comments for DAAAP

Please estimate the expected QT prolongation for the entire range of proposed doses (75 ug q12 h, 150 mcg q 12 h, 300 mcg q12h, 450 mcg q12h, 600 mcg q12h, 750 mcg q12h and 900 mcg q12h) based on the buprenorphine concentration-QTc relationship observed from the data available to the Agency on buprenorphine [REDACTED] (b) (4) for comparison to aid us in our risk-benefit assessment and regulatory decision making. Please recommend language for labeling the QT effect.

QT-IRT's response: According to the exposure-response relationship between buprenorphine concentration [REDACTED] (b) (4)

different QTc effects were predicted in the following table at various interested mean C_{max-ss} concentrations. Because of the uncertainty associated with provided mean C_{max} values, marginal clinically relevant QTc prolongation (comparable to that at (b) (4)) may occur for BEMA with doses of 600 ug q12h or above.

Table 1: Predicted QTc Effects at Various Clinically Relevant Concentrations.

At Interested Mean C_{max-ss} (ng/mL)	Predicted Placebo-Adjusted QTc Change from Baseline (ms)	
	Mean	90%CI upper bound
0.096 at 75 ug q12h of BEMA	0.6226	0.7352
0.196 at 150 ug q12h of BEMA	1.2711	1.5011
0.388 at 300 ug q12h of BEMA	2.5163	2.9715
0.533 at 450 ug q12h of BEMA	3.4567	4.082
0.723 at 600 ug q12h of BEMA	4.6889	5.5371
0.953 at 750 ug q12h of BEMA	6.1806	7.2985
1.121 at 900 ug q12h of BEMA	7.2701	8.5851
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

QT-IRT's proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.

5.7 QTc Prolongation

(b) (4)

12.2 Pharmacodynamics

Effects on Cardiac Electrophysiology (

(b) (4)

BACKGROUND

(b) (4)

Naltrexone appears to blunt the QTc prolongation effect of buprenorphine. The mechanism underlying this finding is unknown.

According to the exposure-response relationship between buprenorphine concentration and QTc, different QTc effects were predicted at various clinically relevant concentrations.

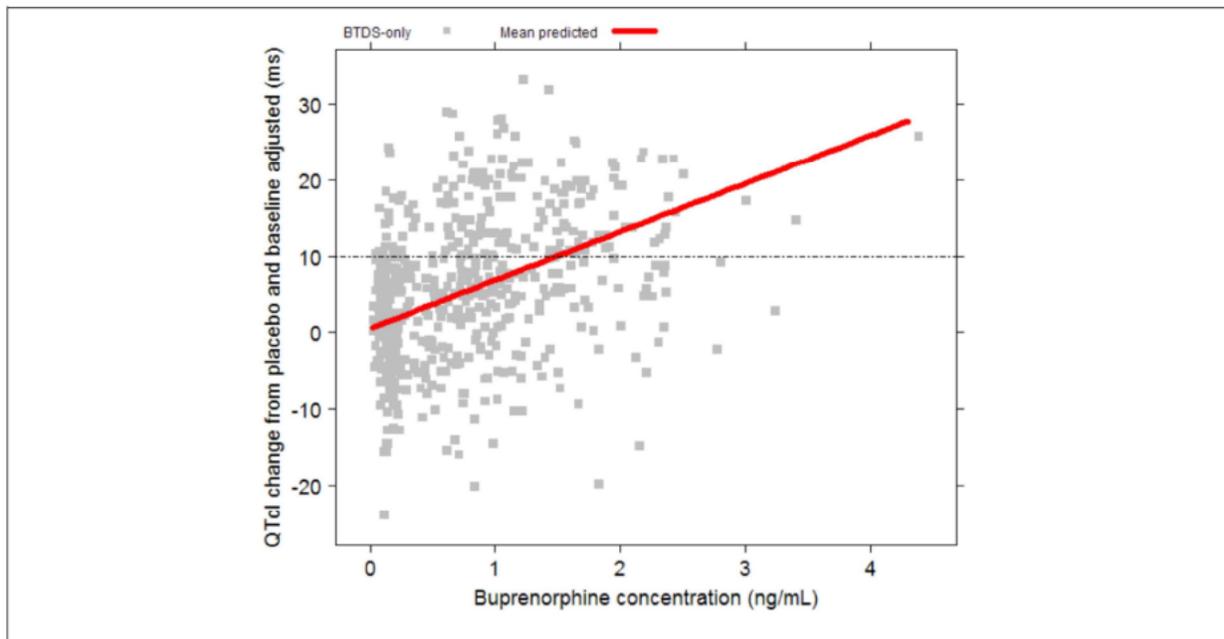
BEMA [®] Buprenorphine dose strength	$C_{\max}^{SS\ddagger}$
150 µg q12h	0.196 (0.034 – 0.225)
300 µg q12h	0.388 (0.078 - 0.399)
450 µg q12h	0.533 (0.121 - 0.454)
600 µg q12h	0.723 (0.059 – 1.624)
750 µg q12h	0.953 (0.062 – 1.359)
900 µg q12h	1.121 (0.106 – 1.200)

Source: Sponsor's response to the division's information request.

Table 24: Exposure-Response Analysis of Buprenorphine Associated with $\Delta\Delta$ QTcI Prolongation

Parameter ($\Delta\Delta$ QTcI = Intercept + slope * Buprenorphine Concentration)	Estimate	P-value	Inter-individual Variability
Intercept (ms)	0 (Fixed)		4.76
Slope (ms per ng/mL)	6.49 (5.31; 7.66)	<.0001	3.8
Residual Variability (ms)	6.41		

Figure 9: Placebo-Corrected Change From Baseline QTcI Versus Buprenorphine Plasma Concentration – Estimates From the Mixed-Effects Model Regression – BTDS Only





Thank you for requesting our input into the development of this product under NDA 207932. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcpqt@fda.hhs.gov

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/s/

JIANG LIU
06/18/2015

NORMAN L STOCKBRIDGE
06/18/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 24, 2015
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 207932
Product Name and Strength:	Belbuca (buprenorphine hydrochloride) buccal film, 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, 900 mcg
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Endo Pharmaceuticals, Inc.
Submission Date:	December 23, 2014
OSE RCM #:	2014-2627
DMEPA Primary Reviewer:	Millie Shah, PharmD, BCPS
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

Endo Pharmaceuticals, Inc. submitted NDA 207932 for Belbuca (buprenorphine hydrochloride) buccal film. Thus, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested we evaluate the container labels, carton labeling, and prescribing information for vulnerabilities that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-(N/A)
ISMP Newsletters	D-(N/A)
FDA Adverse Event Reporting System (FAERS)*	E-(N/A)
Labels and Labeling	F
Highlights of Prescribing and Full Prescribing Information	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container labels, carton labeling, prescribing information, instructions for use, and medication guide to identify deficiencies that may lead to medication errors and other areas for improvement.

Container Labels and Carton Labeling

Our review of the container labels identified areas of improvement to increase clarity and prominence of important information. We note the presence of the statement, "Use entire film. Do not cut, tear, chew, or swallow film." We have post-marketing experience of wrong technique errors with other buccal films, thus we recommend increasing the prominence of this statement to mitigate the risk for wrong technique errors. Thus, we make recommendations in Section 4.2.

Prescribing Information

Our review of the prescribing information determined that the definition of opioid-experienced (or opioid-tolerant) patients is inconsistent with other extended-release/long-acting (ER/LA) opioids, which may lead to confusion. As currently presented, the *Dosage and Administration* section defines opioid-experienced patients as those [REDACTED] (b) (4)

[REDACTED] Other ER/LA opioids define opioid-tolerant (or opioid-experienced) as, “those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, or an equianalgesic dose of another opioid.” A healthcare practitioner may misinterpret the term Morphine Sulfate Equivalents to mean morphine sulfate only and may not consider use of other ER/LA opioids at the doses described above for one week or longer as constituting opioid-tolerance, which may lead to incorrect dosing of Belbuca. Furthermore, the term “opioid-experienced” is used in the prescribing information for Belbuca, whereas other ER/LA opioids use the term “opioid-tolerant,” which may also be a source of confusion. Thus, we recommend the term opioid-experienced and the definition be revised to be consistent with other ER/LA opioids and to mitigate the risk for confusion.

Our review of the *Dosage and Administration* section identified missing units of measure following numbers used to express dose and/or strength and error-prone symbols.

Additionally, we note the statement, [REDACTED] (b) (4) in the *Dosage and Administration* section of the Full Prescribing Information does not match the statement, [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Instructions for Use

Our review of the Instructions for Use (IFU) identified areas of improvement to increase clarity of important information. We note the steps in the IFU are not numbered. We recommend numbering the steps in the IFU to mitigate confusion. Thus, we make this recommendation in Section 4.1. We note the IFU state, “place the yellow side of the BELBUCA against the inside of the moistened cheek.” Although there is risk for wrong technique errors, where patients might place the non-yellow side of the film against the cheek, we determined the IFU clearly presents this step. DMEPA deferred to the clinical review team to determine if placement of the wrong side of the film in the buccal cavity can impact efficacy. In an email dated June 24, 2014, DAAAP stated there is no loss of efficacy if the wrong side of the film is placed in the buccal cavity.

Medication Guide

Our review of the Medication Guide identified an area of improvement to increase clarity of important information. We recommend the statement, “ (b) (4) (b) (4) in the section, “While Using Belbuca” be revised to state, “ (b) (4) (b) (4) remove from the foil and flush down the toilet.” to mitigate the risk for confusion.

4 CONCLUSION & RECOMMENDATIONS

We conclude the Sponsor can improve the proposed labels and labeling to increase clarity and prominence of important information to promote safe use of this product.

If you have further questions or need clarifications, please contact Vaishali Jarral, OSE Project Manager, at 301-796-4248.

4.1 RECOMMENDATIONS FOR THE DIVISION

We have revised the *Dosage and Administration* section of the Highlights of Prescribing and Full Prescribing Information (See Appendix G) and have provided a detailed summary below for review and consideration by DAAAP.

A. Highlights of Prescribing

1. In order to be consistent with other ER/LA opioids and to mitigate the risk for confusion, we recommend the term opioid-experienced be revised to opioid-tolerant. Additionally, we recommend the definition be revised from, (b) (4) (b) (4) to “ (b) (4) (b) (4) (b) (4) (b) (4) If DAAAP decides to use MSE, consider including a dose conversion table for other opioids to morphine sulfate.
2. Units of measure are missing following numbers expressing dose. We recommend adding a unit of measure immediately following all numbers, as appropriate.¹
3. The use of the symbol “<” is error-prone and may be misinterpreted as the opposite of the intended meaning. We recommend replacing the symbol “<” with its full intended meaning, “less than.”²

¹ Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

4. In the Dosage Forms and Strengths section, a comma is missing between the 600 mcg and 750 mcg strengths. We recommend adding a comma between these strengths to mitigate the risk for confusion.

B. Full Prescribing Information

1. See A.1 through A.3.
2. The statement, “(b) (4)” is inconsistent with the statement presented on the principal display panel of the container labels and carton labeling. We recommend revising the statement to read, (b) (4) to maintain consistency and mitigate the risk for confusion.

C. Instructions for Use (IFU)

1. We recommend numbering the steps in the IFU to mitigate the risk for confusion regarding the appropriate sequence of the steps.

D. Medication Guide

1. We recommend revising the statement, (b) (4) “(b) (4)” in the section, “While Using Belbuca” to state, (b) (4) remove from the foil and flush down the toilet.” to mitigate the risk for confusion.

4.2 RECOMMENDATIONS FOR ENDO PHARMACEUTICALS, INC.

We recommend the Sponsor implement the following prior to approval of this NDA.

A. Container Labels (all strengths)

1. Use bold font for the statement, “Use entire film. Do not cut, tear, chew or swallow film” to increase its prominence and mitigate the risk for wrong technique errors.
2. Revise the presentation of the expiration date from “XX/XX/XX” to “MMMYYYY” or “MMMDDYYYY” to mitigate the risk for confusion.³

B. Carton Labeling (all strengths)

1. See A.1 through A.2.

² ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2015 APR 14]. Available at: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

³ Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Belbuca (buprenorphine hydrochloride) buccal film that Endo Pharmaceuticals, Inc. submitted on December 23, 2014.

Table 2. Relevant Product Information for Belbuca (buprenorphine hydrochloride) buccal film	
Initial Approval Date	Not applicable
Active Ingredient	buprenorphine hydrochloride
Indication	management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
Route of Administration	buccal
Dosage Form	buccal film
Strength	75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, 900 mcg
Dose and Frequency	(b) (4)
How Supplied/ Container Closure	cartons containing 60 individual child-resistant foil pouches with one film per pouch
Storage	Store at 25°C (77°F), excursions permitted to 15° to 30°C (59°F to 86°F). [See USP Controlled Room Temperature.]

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On April 9, 2015, we searched the L:drive and AIMS using the term, Belbuca, to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any previous label/labeling reviews relevant to this review.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁴ along with postmarket medication error data, we reviewed the following Belbuca (buprenorphine hydrochloride) buccal film labels and labeling submitted by Endo Pharmaceutical, Inc. on December 23, 2014.

- Container label
- Carton labeling

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⁴ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MILLIE C BRAHMBHATT
04/24/2015

BRENDA V BORDERS-HEMPHILL
04/24/2015

**REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: [NDA 207932](#)

Application Type: [New NDA](#)

Name of Drug/Dosage Form: Belbuca (buprenorphine hydrochloride) buccal

Applicant: Endo Pharmaceuticals, Inc.

Receipt Date: December 23, 2014

Goal Date: October 23, 2015

1. Regulatory History and Applicant's Main Proposals

[Submitted by Endo Pharmaceuticals via 505\(b\)\(2\) pathway, the listed drug is Buprenex \(NDA 018401\) and Subutex \(NDA 020732\)](#)

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

[Note to RPM: See the *SEALD intranet site* for additional PI information including the Labeling Review Tool, labeling regulations and guidances, and the OND labeling review process.](#)

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.
- Comment:**
- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.
- Comment:**
- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
- Comment:**
- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.
- Comment:**
- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.
- Comment:**
- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.
- Comment:**
- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required

Selected Requirements of Prescribing Information

• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

Comment:

- YES** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Selected Requirements of Prescribing Information

Comment:

- YES** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- YES** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES

Selected Requirements of Prescribing Information

21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- YES** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- YES** 36. In the BW, all text should be **bolded**.

Comment:

- YES** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

SPIROS NICOLS
03/06/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 207932	NDA Supplement #: S- N/A	Efficacy Supplement Category: N/A <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric
Proprietary Name: Belbuca Established/Proper Name: buprenorphine hydrochloride Dosage Form: buccal film Strengths: 75mcg, 150mcg, 300mcg, 450mcg, 600mcg, 750mcg, 900mcg		
Applicant: Endo Pharmaceuticals, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: December 23, 2014 Date of Receipt: December 23, 2014 Date clock started after UN: N/A		
PDUFA/BsUFA Goal Date: October 23, 2015		Action Goal Date (if different): October 23, 2015
Filing Date: February 21, 2015		Date of Filing Meeting: February 10, 2015
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input checked="" type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Management of pain severe enough to require daily, around-the clock, long-term opioid treatment and for which alternative treatment options are inadequate.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<i>The application will be a priority review if:</i>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> • <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> • <i>The product is a Qualified Infectious Disease Product (QIDP)</i> • <i>A Tropical Disease Priority Review Voucher was submitted</i> • <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i> 	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): 072428

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>				
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm				
If yes , please list below:				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
NDA 205637	Bunavail	NP	Jun 6, 2017	
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>				
Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>				
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes , # years requested:				
<i>Note: An applicant can receive exclusivity without requesting it;</i>				

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff: 1/6/2015</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

Version: 12/09/2014

7

forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

Version: 12/09/2014

8

Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OMPP\PLT? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent: QT-IRT</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	February 24, 2015

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>DPMH</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 9/14/2010, meeting minutes on 10/18/2010 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 7/15/2014, meeting minutes on 8/6/2014 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 10, 2015

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Spiros Nicols	
	CPMS/TL:		
Cross-Discipline Team Leader (CDTL)	Josh Lloyd		
Division Director/Deputy	Sharon Hertz		
Office Director/Deputy			
Clinical	Reviewer:	Pamela Horn	
	TL:	Josh Lloyd	
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	David Lee	
	TL:	Yun Xu	
Biostatistics	Reviewer:	Kate Meaker, James Travis	
	TL:	Freda Cooner	

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Gary Bond	
	TL:	Dan Mellon, Jay Chang	
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) <i>(for protein/peptide products only)</i>	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Ciby Abraham	
	TL:	Julia Pinto	
Biopharmaceutics	Reviewer:	Fang Wu, Sandra Suarez	
	TL:	John Duan	
Quality Microbiology	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Millie Brahmhatt	
	TL:	Vicky Borders Hemphill	
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines	Reviewer:		
	TL:		
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>It was discussed that the annotated label also referenced (b) (4), and Sponsor did not provide scientific bridge to (b) (4). Comments were sent to Sponsor and the Sponsor addressed the issue adequately by removing all reference to (b) (4) from the label.</p>
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> No comments</p>
<p>CLINICAL</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p>

Comments:	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) 	<input type="checkbox"/> YES

needed?	<input type="checkbox"/> NO
BIostatistics Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (protein/peptide products only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? If no , was a complete EA submitted? If EA submitted , consulted to EA officer (OPS)? Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Quality Microbiology</u> • Was the Microbiology Team consulted for validation of sterilization?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

Comments:	
<u>Facility Inspection</u> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>CMC Labeling Review</u> Comments:	<input type="checkbox"/> Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	

<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Sharon Hertz, MD, Acting Division Director</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): N/A</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments: Mid Cycle meeting on May 21, 2015; Wrap up meeting on September 8, 2015</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and Product

	Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

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

/s/

SPIROS NICOLS
03/17/2015

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: October 19, 2015

To: Spiros Nicols, Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Sharon Hertz, MD, Director - DAAAP

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Jessica Fox, Regulatory Review Officer - OPDP

CC: Olga Salis, Senior Regulatory Project Manager - OPDP

Subject: NDA 207932
Belbuca (buprenorphine) Buccal Film CIII
Professional Labeling Review

As requested in DAAAP's consult dated February 20, 2015, OPDP has reviewed substantially complete prescribing information for Belbuca Buccal Film. The substantially complete prescribing information was provided to OPDP on July 24, 2015 with the file name "Belbuca PI submitted 2-2-15 with FDA tracked changes June 24 2015 to OPDP PLT.docx", and on October 6, 2015 via email by Spiros Nicols with the file name "\\fdsfs01\ode2\DAAAP\NDA and sNDA\NDA 207932 (buprenorphine BELBUCA Endo\Labeling\Sponsor Label resubmitted 29 September 2015\Belbuca Package Insert-Endo Response 9-29-2015-annotated.docx".

OPDP has no comments on the substantially complete prescribing information provided to OPDP on October 6, 2015 as all of the comments we provided to DAAAP on August 5, 2015 on the previous substantially complete prescribing information were addressed in the recent labeling submission.

Please note that comments on the Medication Guide and Patient Instructions for Use was provided under a separate cover as a collaborative review between OPDP and the Division of Medical Policy (DMPP).

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact me at (240) 402-8686 or by email, Koung.Lee@fda.hhs.gov.

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

/s/

KOUNG U LEE
10/19/2015