CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-671

Administrative/Correspondence Reviews

Patent Information

SkyePharma Inc. is submitting information on the following 10 United States patents that cover the formulation, composition or method of use of the drug product, SKY0401:

Patent Number	Patent Expiration Date	Type of Patent	Name of Patent Owner
5,723,147	3/3/15	Formulation	DepoTech Corporation (now SkyePharma Inc.)
5,807,572	9/15/15	Formulation	DepoTech Corporation (now SkyePharma Inc.)
5,891,467	1/31/17	Formulation	DepoTech Corporation (now SkyePharma Inc.)
5,931,809	7/14/19	Formulation	DepoTech Corporation (now SkyePharma Inc.)
5,962,016	11/19/17	Formulation	DepoTech Corporation (now SkyePharma Inc.)
5,997,899	10/1/16	Formulation	SkyePharma Inc.
6,071,534	2/5/18	Formulation	SkyePharma Inc.
US 6,171,613 B1	10/1/19	Formulation	SkyePharma Inc.
US 6,193,998 B1	10/1/19	Formulation	SkyePharma Inc.
US 6,241,999 B1	12/6/19	Formulation	SkyePharma Inc.

Original Declaration

The undersigned declares that Patent No. 5,723,147 covers the formulation, composition, and/or method of use of SKY0401. This product is the subject of this application for which approval is being sought.

Gordon L. Schooley, Ph.D. — Date: 15 Jul 2003

Vice President
Global Clinical Research and Regulatory Affairs
SkyePharma, Inc.

Original Declaration

The undersigned declares that Patent No. 5,807,572 covers the formulation, composition, and/or method of use of SKY0401. This product is the subject of this application for which approval is being sought.

Gordon L. Schooley, Ph.D. — 15 Jul 2003 — Date

Vice President
Global Clinical Research and Regulatory Affairs
SkyePharma, Inc.

Original Declaration

The undersigned declares that Patent No. 5,891,467 covers the formulation, composition, and/or method of use of SKY0401. This product is the subject of this application for which approval is being sought.

Gordon J. Schooley 15 Jul 2003

Gordon L. Schooley, Ph.D. Date
Vice President
Global Clinical Research and Regulatory Affairs
SkyePharma, Inc.

Original Declaration

The undersigned declares that Patent No. 5,931,809 covers the formulation, composition, and/or method of use of SKY0401. This product is the subject of this application for which approval is being sought.

Gordon L. Schooley, Ph.D. — 15 Jul 2003

Gordon L. Schooley, Ph.D.
Vice President
Global Clinical Research and Regulatory Affairs
SkyePharma, Inc.

Date

Original Declaration

The undersigned declares that Patent No. 5,962,016 covers the formulation, composition, and/or method of use of SKY0401. This product is the subject of this application for which approval is being sought.

Gordon J Schooley 15 Jul 2003

Gordon L. Schooley, Ph.D. Date
Vice President
Global Clinical Research and Regulatory Affairs
SkyePharma, Inc.

Original Declaration

The undersigned declares that Patent No. 5,997,899 covers the formulation, composition, and/or method of use of SKY0401. This product is the subject of this application for which approval is being sought.

Gordon L. Schooley, Ph.D. — 15 Jul 2003 — Date

Vice President
Global Clinical Research and Regulatory Affairs
SkyePharma, Inc.

Original Declaration

The undersigned declares that Patent No. 6,071,534 covers the formulation, composition, and/or method of use of SKY0401. This product is the subject of this application for which approval is being sought.

Gordon L. Schooley, Ph.D. — 15 Jul 2003
Date

Vice President
Global Clinical Research and Regulatory Affairs
SkyePharma, Inc.

Original Declaration

The undersigned declares that Patent No. US 6,171,613 B1 covers the formulation, composition, and/or method of use of SKY0401. This product is the subject of this application for which approval is being sought.

15 Jul 2003

Gordon L. Schooley, Ph.D.
Vice President
Global Clinical Research and Regulatory Affairs
SkyePharma, Inc.

Date

Original Declaration

The undersigned declares that Patent No. US 6,193,998 B1 covers the formulation, composition, and/or method of use of SKY0401. This product is the subject of this application for which approval is being sought.

Gordon L. Schooley, Ph.D. — Date: 15 Jul 2003

Vice President
Global Clinical Research and Regulatory Affairs
SkyePharma, Inc.

Original Declaration

The undersigned declares that Patent No. US 6,241,999 B1 covers the formulation, composition, and/or method of use of SKY0401. This product is the subject of this application for which approval is being sought.

Gordon L. Schooley, Ph.D.
Vice President
Global Clinical Research and Regulatory Affairs
SkyePharma, Inc.

15 Jul 2003
Date

Paragraph I Patent Certification Statement

In the opinion of SkyePharma, Inc. and to the best of our knowledge, there are no current patents on the listed drug substance, morphine sulfate, for which patent certification is required in accordance with 21 U.S.C. 355(b) or (c).

Gordon L. Schooley, Ph.D. — Date: 15 Jul 2003

Gordon L. Schooley, Ph.D.
Vice President
Global Clinical Research and Regulatory Affairs
SkyePharma, Inc.

EXCLUSIVITY SUMMARY FOR NDA # 21-671

Trade Name DepoDur Generic Name: Morphine sulfate extended-release liposome injection

Applicant Name: SkyePharma HFD # 170

Approval Date If Known May 18, 2004

PART I-- IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES /__X_/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8.

It is a 505(b)(2).

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

NA

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

NA

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

___NA_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

Note: A PWR for the moiety (intravenous morphine sulfate for moderate to severe pain in pediatric patients) has been submitted to NIH for funding through their program.

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II -- FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other

esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /__X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III -- THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /__X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /__X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X__/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Study to Evaluate the Safety and Efficacy of a Single Epidural Dose of Sustained-Release Encapsulated Morphine (SKY0401) in the Management of Post-Operative Pain in Patients Undergoing Hip Arthroplasty

A Phase 3, Randomized, Double-Blind, Dose-Controlled, Parallel Group, Dose-Ranging Study to Evaluate the Safety and Efficacy of a Single Epidural Dose of Sustained-Release Encapsulated Morphine (SKY0401) in the Management of Post-Operative Pain in Patients Undergoing Lower Abdominal Surgery

A Randomized, Double-Blind, Active-Controlled, Dose-Ranging, Parallel Group Study to Evaluate the Safety and Efficacy of a Single Epidural Dose of Sustained-Release Encapsulated Morphine (SKY0401) in the Management of Post-Operative Pain in Patients Undergoing Elective Cesarean Section under Intrathecal Anesthesia

Studies comparing two products with the same ingredient(s) are considered to be bioavailability

studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_NA_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_NA_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Study to Evaluate the Safety and Efficacy of a Single Epidural Dose of Sustained-Release Encapsulated Morphine (SKY0401) in the Management of Post-Operative Pain in Patients Undergoing Hip Arthroplasty

A Phase 3, Randomized, Double-Blind, Dose-Controlled, Parallel Group, Dose-Ranging Study to Evaluate the Safety and Efficacy of a Single Epidural Dose of Sustained-Release Encapsulated Morphine (SKY0401) in the Management of Post-Operative Pain in Patients Undergoing Lower Abdominal Surgery

A Randomized, Double-Blind, Active-Controlled, Dose-Ranging, Parallel Group Study to Evaluate the Safety and Efficacy of a Single Epidural Dose of Sustained-Release Encapsulated Morphine (SKY0401) in the Management of Post-Operative Pain in Patients Undergoing Elective Cesarean Section under Intrathecal Anesthesia

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1-#3

IND # 52,113 YES /__X_/ ! NO /___/ Explain: _____

Note: In a submission dated June 17, 1999 to IND 52,113, the sponsor changed their corporate name from DepoTech Corporation to SkyePharma.

(b) For each investigation not carried out under an IND or for which the applicant was not

identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /__X_/

If yes, explain:

Signature: Sara E. Stradley, MSc 5/18/04
Title: Regulatory Project Manager
Concurred by Parinda Jani
Title: CPMS, 5/18/04

Signature: Bob Rappaport, MD
Title: Division Director

Form OGD-011347 Revised 05/10/2004
cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

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

/s/

Bob Rappaport
5/18/04 08:28:09 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-671 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: July 18, 2003 **Action Date:** May 18, 2004

HFD -170 **Trade and generic names/dosage form:** DepoDur (morphine sulfate extended-release lipsome injection) 10mg/mL

Applicant: SkyePharma, Inc. **Therapeutic Class:** S3

Indication(s) previously approved: NA

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: extended-release liposome injection for the administration by the epidural route at the lumbar levels for the treatment of pain following major surgery.

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

- X **No: Please check all that apply:** ____**Partial Waiver** __X__**Deferred** ____**Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**

- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred: all ages under 18 years of age

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- **X Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): **June 2008**

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-671
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: NA

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: **NDA 21-671**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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

/s/

Sara Stradley
5/18/04 03:59:32 PM

Debarment Certification Statement

SkyePharma Inc. 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.

Gordon L. Schooley, Ph.D. — 15 Jul 2003

Gordon L. Schooley, Ph.D.
Vice President
Global Clinical Research and Regulatory Affairs
SkyePharma, Inc.

Date

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)443-3741

DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVAL ACTION

DATE:	May 18, 2004
DRUG:	DEPODUR (morphine sulfate extended-release liposome injection) 10 mg/mL
NDA:	21-671
NDA Code:	Type 3S NDA
SPONSOR:	SkyPharma, Inc.
INDICATION:	For the treatment of pain following major surgery

SkyPharma, Inc. has submitted NDA 21-671 in support of marketing approval for their extended-release liposomal injectable formulation of morphine sulfate. This product is indicated for epidural injection to provide post-operative analgesia after major surgical procedures performed below the umbilicus.

Review of the CMC portion of this application was completed by Michael C. Theodorakis, Ph.D. Review of the pharmacology and toxicology data presented in this application was completed by Mamata De, Ph.D. Review of the clinical pharmacology and biopharmaceutics data in the application was completed by David Lee, Ph.D. A statistical review and evaluation was completed by Dionne L. Price, Ph.D. Consultation on this application was obtained from the microbiology section of OPS, the Division of Drug Marketing, Advertisement and Communications, the Controlled Substance Staff and the Office of Drug Safety. The sponsor has submitted five studies in support of efficacy. A detailed review of these studies and of the safety of the product was performed by Lester Schultheis, M.D.

Efficacy:

The sponsor denoted five studies (SKY0401-009, SKY0401-011, SKY0401-012b, SKY0401-015 and SKY0401-017) as pivotal in support of a finding of efficacy.

Study SKY0401-009 (009) was a multicenter, randomized, placebo-controlled, double-blind, parallel-group study comparing DEPODUR doses of 10, 20 and 30 mg to placebo for the treatment of post-operative pain in subjects undergoing hip arthroplasty under general anesthesia. A standardized regimen of general anesthesia was used during the procedure. A single dose of 10, 20, or 30mg of DEPODUR or placebo (DepoFoam liposomal particles without morphine sulfate) was administered epidurally prior to the induction of general anesthesia, approximately 30 minutes prior to the initiation of the surgery. A test dose of 3 mL of 2% lidocaine with 1:200,000 epinephrine was injected just prior to study drug administration to detect inadvertent intravascular or intrathecal injection.

After the surgery, the patients were instructed to request analgesic treatment when their pain changed from mild to moderate. A dose of 25 mcg of fentanyl was administered intravenously to patients at that time and repeat doses were administered until satisfactory pain relief was achieved. Subsequently, patients were permitted to self-administer IV fentanyl via a patient-controlled analgesia (PCA) pump to maintain satisfactory pain control. A basal infusion of IV fentanyl was added as necessary. After 48 hours, patients were administered alternative narcotic analgesics at the discretion of the investigators. Naloxone was administered as necessary for the treatment of opiate-related adverse events.

The primary efficacy variable was defined as the total quantity of fentanyl used during the 48 hours following the administration of study drug.

Secondary efficacy measures included:

- Proportion of patients receiving no fentanyl (or other narcotic analgesic) from 0 to 24, greater than 24 to 48, and 0 to 48 hours
- Time between the dose of study drug and the first dose of fentanyl or other narcotic analgesic
- Time between recovery room arrival and first dose of fentanyl to control post-operative pain
- Resting pain intensity measured by VAS and categorical scale at the time of the first dose of fentanyl or other narcotic analgesic
- Pain intensity at rest and with activity measured by VAS and categorical scale at multiple time points post-operatively

- Patient-rated overall assessment of study medication at 24, 48 and 72 hours after administration of study drug

One hundred twenty-six subjects were enrolled in the study at 13 study sites. Of the 126 subjects enrolled, 120 received study drug.

Dose	N
10 mg	35
20 mg	32
30 mg	26
Placebo	27

One patient (03-004) was randomized to placebo but received 10-mg DEPODUR. This subject was included in the 10-mg group for all efficacy analyses except for the ITT primary efficacy analysis for which he was included in the placebo group.

All subjects were included in the efficacy analyses. Approximately 10% of patients received a narcotic analgesic other than fentanyl prior to 48 hours post-operatively. However, evaluation of the doses of analgesic administered to these patients and of the distribution of these patients indicated that these protocol violations did not significantly impact on the efficacy analyses.

The primary efficacy analysis performed on the ITT population demonstrated a dose-related treatment effect for all three dose-groups of DEPODUR compared to placebo. A per-protocol analysis that included Subject 03-004 in the 10-mg DEPODUR group demonstrated comparable results to the ITT analysis.

Mean Total Fentanyl Use (mcg) 0 to 48 Hours, ITT Analysis

Dose Group	Total Fentanyl
Placebo	2434
10 mg	1321
20 mg	905
30 mg	652

$p < 0.001$

The results of the secondary efficacy analyses were essentially supportive of a significant treatment effect for DEPODUR compared to placebo.

Study SKY0401-011 (011) was a multicenter, randomized, placebo-controlled, double-blind, parallel-group study comparing DEPODUR doses of 15, 20 and 25 mg to placebo for the treatment of post-operative pain in subjects undergoing hip arthroplasty under

standardized general or regional anesthesia. A single dose of 15, 20, or 25mg of DEPODUR or placebo (preservative-free 0.9% normal saline) was administered epidurally prior to the induction of general anesthesia, approximately 30 minutes prior to the initiation of the surgery. A test dose of 3 mL of 2% lidocaine with 1:200,000 epinephrine was injected just prior to study drug administration at the discretion of the investigator to detect inadvertent intravascular or intrathecal injection.

After the surgery, the patients were instructed to request analgesic treatment when their pain changed from mild to moderate. A dose of 25 mcg of fentanyl was administered intravenously to patients at that time and repeat doses were administered until satisfactory pain relief was achieved. Subsequently, patients were permitted to self-administer IV fentanyl via a patient-controlled analgesia (PCA) pump to maintain satisfactory pain control. After 48 hours, patients were administered alternative narcotic analgesics at the discretion of the investigators. An opiate antagonist was administered as necessary for the treatment of opiate-related adverse events.

The primary efficacy variable was defined as the total quantity of fentanyl used during the 48 hours following the administration of study drug.

Secondary efficacy measures included:

- Time to first post-operative fentanyl use
- Proportion of patients receiving no fentanyl post-operatively
- Activity score
- Pain intensity measured with a VAS
- Pain intensity measured with a categorical scale
- Patient rating of pain medication
- Surgeon rating of pain medication

Two hundred subjects were enrolled in the study at 23 study sites. Of these 200 patients, 194 constituted the ITT population. Five subjects were not included in the ITT population because no data was collected on the use of fentanyl or other opiate medications and the remaining subject did not have surgery.

Dose	N
15 mg	51

20 mg	50
25 mg	49
Placebo	50

The primary efficacy analysis performed on the ITT population demonstrated a dose-related treatment effect for all three dose-groups of DEPODUR compared to placebo.

Mean Total Fentanyl Use (mcg) 0 to 48 Hours, ITT Analysis

Dose Group	Total Fentanyl
Placebo	2091
15 mg	663
20 mg	485
25 mg	371

$p < 0.0001$

Of note, Dr. Schultheis has assessed the differences between the DEPODUR treatment groups as modest from a clinical perspective. There was a 150-mcg difference between the median 15-mg dose and the 20-mg dose (178 mcg for the mean doses), and a 0 difference between the median 20-mg and 25-mg doses (114 mcg for the mean doses). Dr. Schultheis states that a difference of approximately 150 mcg of fentanyl administered over 48 hours is unlikely to be of real clinical significance.

The results of the secondary analyses of efficacy essentially supported the finding of a significant treatment effect for DEPODUR at all doses compared to placebo. However, the results for the activity scores were not statistically significant between the treatment groups. Also, although the pain intensity categorical scales, both with activity and at rest, were statistically significantly different between the treatment groups at 24 hours, they were not statistically significantly different at 48 hours.

Study SKY0401-012b (012b) was a multicenter, randomized, dose- and active-controlled, double-blind, parallel-group study comparing DEPODUR doses of 10, 15, 20

and 25 mg to DEPODUR 5 mg and to MS IR 5 mg for the treatment of post-operative pain in subjects undergoing lower abdominal surgery under general or regional anesthesia. A single dose of 5, 15, 20, or 25mg of DEPODUR or 5 mg of MS IR was administered epidurally prior to the induction of general anesthesia, approximately 30 minutes prior to the initiation of the surgery. A test dose of 3 mL of 2% lidocaine with 1:200,000 epinephrine was injected just prior to study drug administration at the discretion of the investigator to detect inadvertent intravascular or intrathecal injection.

Post-operatively, patients were permitted to self-administer IV fentanyl via a patient-controlled analgesia (PCA) pump to maintain satisfactory pain control from the time of their first request for pain treatment. After 48 hours, patients were administered alternative narcotic analgesics at the discretion of the investigators. Opiate antagonists were administered as necessary for the treatment of opiate-related adverse events.

The primary efficacy variable was defined as the total quantity of fentanyl used during the 48 hours following the administration of study drug.

Secondary efficacy measures included:

- Time to first post-operative fentanyl use
- Proportion of patients receiving no fentanyl post-operatively
- Pain intensity evaluation using a VAS
- Pain intensity evaluation using a categorical scale
- Patient rating of pain medication
- Surgeon rating of pain medication

The original protocol called for a placebo arm and four DEPODUR arms. Amendment 2 replaced the placebo arm with a 5-mg DEPODUR-dose group and an immediate-release morphine sulfate-dose (IR MS) group. Five hundred forty-six subjects were enrolled in the study at 51 study sites. Of the 546 subjects enrolled, 498 were randomized after implementation of Amendment 2, but only 487 underwent their surgical procedures. These 487 subjects constituted the ITT population.

Dose	N
5 mg	86
10 mg	70
15 mg	84

20 mg	79
25 mg	83
5-mg IR MS	85

All ITT subjects were included in the efficacy analyses. Five patients were randomized to the placebo arm prior to Amendment 2. These subjects were not included in the ITT population.

The primary efficacy analysis performed on the ITT population demonstrated a dose-related treatment effect for the 10-mg, 15-mg, 20-mg, and 25-mg DEPODUR dose groups compared to the 5-mg DEPODUR dose group. The sponsor performed two different analyses of the data. The first was a linear regression analysis (requested by the Division) of dose-related reduction in post-operative IV fentanyl use through 48 hours after study drug administration. This analysis demonstrated a statistically significant treatment effect with a p-value of 0.0002. (See Figure 1.5.3.1, page 55 of Dr. Schultheis' review)

The sponsor's second analysis demonstrated a statistically significant reduction in mean total IV fentanyl use through 48 hours.

Mean Total Fentanyl Use (mcg) 0 to 48 Hours, ITT Analysis

Dose Group	Total Fentanyl
5mg	1213
10 mg	995
15 mg	959
20 mg	972
25 mg	683
5-mg IR MS	1218

p = 0.005	overall pairwise comparison to 5-mg DEPODUR
p = 0.001	overall pairwise comparison to 5-mg MS IR

Of note, Dr. Schultheis again assessed the differences between the DEPODUR treatment groups as modest from a clinical perspective. The median difference in total fentanyl use over 48 hours between the 10-mg group and the 25-mg group was only 145 mcg.

Narcotics other than fentanyl were used to supplement analgesia during the 48 hours after surgery. Total narcotic analgesic doses were transformed to fentanyl equivalents using a protocol-specified paradigm. Although not a protocol-specified analysis, comparison of the fentanyl-equivalent doses between the treatment groups demonstrated statistically significantly lower mean total drug use for the 15-, 20- and 25-mg DEPODUR-dose groups compared to the MS IR-dose group.

The results of the secondary endpoint analyses were generally supportive of the product's efficacy. However, for the "time to first post-operative IV fentanyl use," not clinically relevant or statistically significant differences were found between any of the treatment arms. Also, while the results for the other secondary endpoints consistently trended in the direction of superior analgesia in the DEPODUR group, not all of the differences were statistically significant.

Study SKY0401-015 (015) was a multicenter, randomized, active-controlled, double-blind, parallel-group study comparing DEPODUR doses of 5, 10 or 15 mg to 5 mg of MS IR for the treatment of pain in women undergoing cesarean section with intrathecal anesthesia consisting of bupivacaine and fentanyl. A single dose of 5, 10 or 15 mg of DEPODUR or 5-mg MS IR was administered epidurally following delivery and clamping of the umbilical cord.

Following surgery, subjects were administered analgesia at the discretion of the investigator. Allowed analgesics included acetaminophen with codeine, IV morphine by intermittent bolus injection, or IV morphine via PCA. However, some patients received oxycodone or hydrocodone preparations in violation of the protocol.

The primary efficacy variable was defined as the total quantity of narcotic analgesic (in IV morphine equivalents) used during the 48 hours following the administration of study drug.

Secondary efficacy measures included:

- Total amount of IV opiate analgesic administered
- Time to first post-operative opiate analgesic use
- Proportion of patients receiving no IV opiate analgesic post-operatively
- Proportion of patients receiving no opiate analgesic post-operatively
- Pain intensity evaluation using a VAS
- Pain intensity evaluation using a categorical scale
- Functional ability scores
- Patient rating of pain control

Seventy-nine subjects were enrolled in the study at 4 study sites. Of the 79 subjects enrolled, 75 had surgery and completed the 48-hour observation period. These 75 subjects constituted the ITT population.

Dose	N
5 mg	19
10 mg	19
15 mg	19
5-mg IR MS	18

All ITT subjects were included in the efficacy analyses.

The primary efficacy analysis performed on the ITT population demonstrated a dose-related treatment effect for all three dose-groups of DEPODUR compared to MS IR.

Dose	Total opiate administered (MS IV equivalents)
5 mg	35
10 mg	25
15 mg	29
5-mg IR MS	47

$p = 0.02$ (overall pairwise comparison)

The sponsor performed a secondary analysis on the primary efficacy data. This analysis evaluated total opiate analgesic use over 24-hour intervals. The results of the analysis demonstrated a statistically significant treatment effect for the 10- and 15-mg groups from greater than 24 to 48 hours. The differences were not statistically significantly different for the 5-mg group during that time interval or for any of the groups during the 0 to 24 hour time interval.

The results of the secondary endpoint analyses were mixed, with most of the analyses generally supportive of the product's efficacy.

Study SKY0401-017 (017) was a multicenter, randomized, placebo-controlled, double-blind, parallel-group study comparing DEPODUR doses of 20 and 30 mg to sham epidural for the treatment of post-operative pain in subjects undergoing knee arthroplasty under general or regional anesthesia. A standardized regimen of general anesthesia was used during the procedure. A single dose of 20, or 30mg of was administered epidurally prior to the induction of anesthesia, approximately 30 minutes prior to the initiation of

the surgery. A test dose of 3 mL of 1.5% lidocaine with 1:200,000 epinephrine was injected just prior to study drug administration at the discretion of the investigator to detect inadvertent intravascular or intrathecal injection. Subjects in the placebo group received a sham epidural injection.

After the surgery, patients in the DEPODUR groups received IV hydromorphone administered at the first request for pain medication until the pain was controlled. A PCA pump delivering normal saline was then set up and the "dose" was increased as needed. Hydromorphone 0.2 mg/ml was administered with each PCA dose increase. Patients in the placebo (sham epidural) group received IV morphine until pain was controlled and then permitted to self-administer IV MS via a PCA pump as needed.

The primary efficacy variable was defined as a time-weighted pain intensity recall score (VAS) averaged over 48 hours.

Secondary efficacy measures included:

- Pain intensity at rest using a VAS
- Pain intensity at rest using a categorical scale
- Pain intensity with activity using a VAS
- Pain intensity with activity using a categorical scale
- Physical therapist's rating of patient's ability to tolerate physical therapy
- Patient's rating of overall pain control
- Range of motion
- Use of physical support

One hundred sixty-eight subjects were enrolled in the study at 16 study sites. Of the 186 subjects enrolled, 164 received study drug and had at least two post-randomization assessments. These 164 subjects constituted the ITT population.

Dose	N
20 mg	58
30 mg	51
Sham epidural	55

The primary efficacy analysis performed on the ITT population demonstrated no statistically significant treatment effect. However, the pain intensity scores were reduced in a dose-dependent manner with DEPODUR treatment compared to placebo (sham epidural).

Dose Group	VAS
Sham epidural	39
20 mg	35
30 mg	32

p = 0.09

The results of the secondary efficacy analyses were essentially supportive of a treatment effect for DEPODUR compared to placebo. However, there were no significant differences between the DEPODUR groups and the control group for the range of motion evaluation, the physical therapist's rating and the use of physical support.

Clinical Safety:

A total of 961 subjects were exposed to DEPODUR during the clinical development program at doses from 2.5 to 40 mg. Thirty-four of those subjects were normal

volunteers. The subjects were reasonably well distributed over the dosage groups 5 through 30 mg.

Five patients died during the studies, including the 30-day follow-up period. Only one of those patients appeared to have died as a result of DEPODUR exposure. This elderly, male patient was administered 20 mg of DEPODUR for a planned lower abdominal procedure. However, the procedure was not performed as the pre-incision colonoscopy revealed that there was no tumor. Approximately 21 hours later the patient was found unresponsive with emesis in his airway.

One or more SAEs were reported for 11% of all DEPODUR-treated subjects, compared to 5%, 6% and 9% for placebo (DepoFoam without MS or saline), epidural MS IR and sham epidural-treated patients, respectively. The most common (greater than or equal to 0.3% incidence) SAEs in DEPODUR-treated patients were paralytic ileus, respiratory depression, myocardial infarction, pulmonary embolism, hypoventilation, urinary retention, somnolence, cellulites, gastrointestinal hemorrhage, atrial fibrillation, cardiac arrest, hypotension, post-operative would infection, joint dislocation and pyrexia. None of these events would be considered unusual in this patient population and none occurred with an unusually high incidence.

The adverse events that resulted in study discontinuation did not appear to be related to study drug.

Dr. Schultheis took a closer look at the respiratory event profile for the studies. While the incidence of serious respiratory events for doses of 15 mg or less was no different from the comparator treatments, for all of the episodes of respiratory depression that did occur, 4% of the DEPODUR-treated patients required treatment with a narcotic antagonist compared to 0.4% of patients administered alternative treatments. The incidence of serious respiratory events in the DEPODUR groups also appeared to be dose related, especially at doses of 20 mg and above.

One case of lower extremity weakness occurred in a 68 year-old man after he underwent a radical prostatectomy. He received a 10-mg dose of DEPODUR prior to the procedure. The weakness resolved over the next week. A relationship to DEPODUR cannot be excluded.

The common adverse events seen with exposure to all doses of DEPODUR were those that would be expected with administration of a potent opiate analgesic.

Nonclinical Safety:

Based on her review of the nonclinical safety data submitted to the application, Dr. De has determined that the NDA provides an adequate preclinical safety profile to support

approval for clinical use, with appropriate labeling. The nonclinical development program relied in part on the Agency's approval of two other applications. One of those applications was DepoCyt (NDA 21-041), a product owned by SkyePharma, and the other was Duramorph (NDA 18-565). The sponsor has certified that there are no patents listed for Duramorph. Data regarding genotoxicity and reprotoxicity of morphine is widely available in the literature and that data was also used in Dr. De's review.

Dr. De has recommended one Phase 4 commitment. Tricaprylin, one of the excipients in DEPODUR, has only been qualified for epidural administration in dogs. The safety margin for this inactive ingredient was 1000-fold based on intravenous rat data. As such, it is unlikely to cause toxicity in humans. However, to provide more complete assurance, another epidural study should be performed in a second species.

[ ] an impurity [ ] has been found in the drug substance used in the preparation of this product. As these types of structures are thought to be potential genotoxins/carcinogens, the sponsor will need to perform genetic toxicology studies on the impurity. If those studies demonstrate positive or equivocal results, the impurity should be reduced to acceptable levels or qualified in a carcinogenicity study. The sponsor has agreed to interim specifications suggested by the Nonclinical Safety and the CMC teams.

Biopharmaceutics:

Concerns were raised during the course of the review by Dr. Lee and the CMC team that the specifications for the *in vitro* release testing of the product may be inadequate to provide safe use of DEOPDUR due to possible delayed dose-dumping of morphine into the intrathecal space. Dr. Lee's review recommends that the sponsor submit further data to justify their *in vitro* release method and specifications as a Phase 4 commitment. However, the clinical team noted that the available safety data with over 900 subjects followed for 30 days did not reveal any evidence of delayed dose-dumping. Delayed respiratory depression following intrathecal morphine injection is a well-recognized concern that could be delayed even a few days further with DEPODUR in susceptible patients. This can be addressed with appropriate warnings in the package insert. In addition, further discussion between the CMC team and the sponsor after Dr. Lee's review was filed resulted in an agreement between the sponsor and the Division that they will tighten their *in vitro* release specifications on an interim basis and that they will revise those specifications as appropriate following manufacturing of — additional batches.

Chemistry, Manufacturing and Controls:

Dr. Theodorakis has determined that the drug product quality, purity and controls are adequate for safe distribution. The sponsor has agreed to submit supplements to the

NDA that will provide a new methodology to [redacted] determination in the drug product, limit the amount of the [redacted] impurity, and reevaluate and change the *in vitro* release specifications based on data from the first [redacted] commercial batches. In addition, they have agreed to [redacted] during product manufacturing and to submit timeframes for conducting and reporting on the studies within 30 days of product approval.

Discussion:

The sponsor has demonstrated that their product, DEPODUR, is safe and effective when used according to the product labeling. The risks of dose-related and late onset respiratory depression, and the need for increased vigilance in certain patient populations, particularly those that receive DEPODUR and then have their surgery canceled, have been appropriately addressed in the agreed upon labeling.

Dr. Schultheis performed an analysis of the risk to benefit of the dose response relationship for DEPODUR compared with the adverse event profile at increasing doses of the product. Based on that review, he determined that the 15-mg starting dose initially recommended by the sponsor for patients undergoing lower abdominal surgery did not demonstrate a clinically relevant improvement over the 10-mg dose, particularly in light of the dose-related increasing incidence of respiratory depression. Nevertheless, it is expected that some patients will require higher doses than others based on weight, age, comorbidity and concomitant medications. Therefore, the Dosing and Administration section of the label has been written to allow prescriber discretion in dosing.

This application was filed under section 505(b)(2) of the Act. The only discipline that relied upon literature or a previous agency finding of safety or effectiveness to establish the safety or efficacy of this product was the pharmacology/toxicology team. The review by Dr. De references NDA 21-041 for DepoCyt in the evaluation of the toxicity of the liposomal component of the product, but this NDA is owned by SkyePharma. Her review also references NDA 18-565 for Duromorph in the evaluation of the basic pharmacology of intrathecal morphine administration, and general toxicology data for morphine. The sponsor has certified that there are no patents listed for Duromorph.

The clinical section of the application was complete and did not require reference to any approved drug product or to my determination of the safety and efficacy of the product. The package included adequate and well-controlled clinical trials and a safety database that was considered by the review team to be appropriately sized for this product.

Action taken by the Division: Approval

Bob A. Rappaport, M.D.
Director
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II, CDER, FDA

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

/s/

Bob Rappaport
5/18/04 08:37:56 PM
MEDICAL OFFICER

SkyePharma

May 17, 2004

Bob Rappaport, M.D.
Director
Division of Anesthetic, Critical Care and
Addictive Drug Products (HFD-170)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Attention: Division Document Room, 8B-45

Subject: **DepoDur™ (morphine sulfate extended-release liposome injection)**
New Drug Application (NDA) 21-671
Amendment to Pending Application: Written Agreements and Commitments

Dear Dr. Rappaport,

The purpose of this submission is to provide written agreements and commitments in reply to several outstanding items regarding NDA 21-671 that were received via e-mail from Sara Stradley on May 17, 2004. Reference is made to the original electronic NDA for DepoDur submitted on July 18, 2003.

The Agency comments are provided below (in bold-faced type), and SkyePharma's response follows each comment:

1. The package and container labeling has the established name as [redacted] " The approved name has "extended-release" [redacted]
You will need to modify the package and container label.

SkyePharma agrees to revise the package and container labeling so that the proprietary and established names are shown as follows: DepoDur™ (morphine sulfate extended-release liposome injection).

2. The "Request for Deferral of Pediatric Studies" notes (p. 2) that the peds plan will be discussed with the Agency after approval for adults and that you plan to submit testing in peds patients within 2 years after approval in adults. We need to have a specific date for the protocol submission, study completion and report submission. You will need to make a proposal and submit to us.

The pediatric protocol will be submitted in September 2004. Per the Agency's commitment during today's telecon, SkyePharma requests discussions to decide upon the final pediatric clinical trial design. Assuming an open-label safety study, SkyePharma expects to complete the study by March 2006 with submission of the clinical study report May 2006. Assuming an efficacy and safety trial of DepoDur in pediatric patients of all age ranges i.e., neonates through adolescents, SkyePharma expects to complete the study by February 2008 with final clinical study report submitted by June 2008.

SkyePharma Inc. 10450 Science Center Drive, San Diego, California 92121, USA
Tel (858) 625 2424 Fax (858) 625 2439 www.skyepharma.com

3. We also need you to agree to an educational program during roll-out.

SkyePharma hereby agrees to an educational program during roll-out. Per the Agency's request, the educational program will include a focus for both pharmacists and practitioners on eliminating medication errors.

4. Phase 4 nonclinical commitment: Tricaprylin, an inactive ingredient, has been adequately qualified for epidural administration on only one species. The current practice in CDER follows the draft guidance on inactive ingredients and recommends that new excipients be qualified in two species, at least one non-rodent. As a Phase 4 Commitment, the Sponsor should complete a 28-day epidural repeat-dose toxicity study in a second species. The study protocol may mimic study 033-00009 (DepoFoam Encapsulated Morphine Sulfate (C0401): A Bolus Epidural Multiple-Dosing Toxicity Study in the Beagle Dog). The study should either use the final clinical formulation of DepoDur or the isolated tricaprylin component.

SkyePharma commits to performing a 28-day epidural repeat-dose toxicity study in a second species. The study will be initiated as soon as test article is available (no later than October 2004). It is anticipated that the final study report will be submitted no later than May 2005.

5. DepoDur Package Insert

SkyePharma hereby agrees to the package insert (attached) that was also agreed in a telecon on May 17, 2004.

If you have any questions regarding this submission, please contact Paula Adams, Ph.D. by telephone at (858) 625-2414 ext. 3215 or by fax at (858) 558-6617.

Sincerely,

Steven W. Jensen
Director, Regulatory Affairs

REQUEST FOR DEFERRAL OF PEDIATRIC STUDIES

IND: 52,113
NDA: 21-671
Sponsor: SkyePharma Inc.
Indication: management of post-operative pain

(a) Is the indication for a life-threatening condition that occurs in the pediatric population?

Yes ☐ No ☒

(b) If yes, are there approved therapies labeled for use in the pediatric population?

Yes ☐ No ☐ Not applicable ☒

(c) If yes, list the approved therapies and labeled pediatric age group(s) of approval.

Not applicable

1. What ages are included in your deferral request?

All ages under 18.

Reason for not including the entire pediatric population in the studies or in the deferral request:
☐ Adequate pediatric labeling
☐ Studies Completed in Ages
☐ Requesting a waiver
☐ Other
☐ Currently conducting pediatric studies that will be submitted with application

2. Reason(s) for deferring pediatric studies:

☒ Adult studies completed and ready for approval
☐ Additional postmarketing safety data needed
☐ Technological problems with development of a pediatric formulation (provide documentation)
☐ Difficulty in enrolling pediatric patients (provide documentation)
☐ Other (specify)

Explanation: Deferral of pediatric studies was discussed with the Division during the End of Phase 2 meeting. The Division agreed that pediatric studies should be deferred until after SKY0401 approval in the adult population.

3. Have pediatric drug development plans been submitted to the Agency?

   Yes ☐ No ☒

   If yes, date submitted.
   If no, projected date pediatric plan is to be submitted.

   Pediatric plans will be discussed with the agency after SKY0401 approval in the adult population.

4. Suggested deferred date for submission of studies.

   We plan to submit results of testing in pediatric patients within 2 years after SKY0401 is approved in the adult population.

SkyePharma

May 14, 2004

Bob Rappaport, M.D.
Director
Division of Anesthetic, Critical Care and
Addictive Drug Products (HFD-170)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Attention: Division Document Room, 8B-45

Subject: **SKY0401 (Morphine Sulfate Sustained-Release Liposome Injection)**
New Drug Application (NDA) 21-671
Amendment to Pending Application: Response to CMC Questions
Received May 13, 2004

Dear Dr. Rappaport,

The purpose of this submission is to provide written agreements and responses to the list of CMC questions received via e-mail from Sara Stradley on May 13, 2004. Reference is made to the original electronic NDA for SKY0401 submitted on July 18, 2003.

The questions are provided below (in bold-faced type), and SkyePharma's response follows each question:

1. Provide a certification from your vendor [redacted]

SkyePharma has included copies of letters from its [redacted] suppliers in NDA section 3.2.A.2[redacted], certifying that the [redacted] they produce complies with the European (EU) Committee for Proprietary Medicinal Products (CPMP) guidance on minimizing the risk of transmitting animal spongiform encephalophathy (TSE) agents via human and veterinary medicinal products. [redacted]

[redacted] The Committee also lists in its "draft requirements for sourcing from well-monitored herds materials intended to be used for the manufacture of human and veterinary products" that one of the "criteria for well-monitored herds include having had no cases of TSE".

SkyePharma Inc. 10450 Science Center Drive, San Diego, California 92121, USA
Tel (858) 625 2424 Fax (858) 625 2439 www.skyepharma.com

With this clarification, it is SkyePharma's understanding that the certificates previously supplied to the Agency comply with the request to provide evidence [

].

2. Provide the LOD and LOQ for the cholesterol testing method.

The estimated LOD and LOQ for the determination of cholesterol in SKY0401 is — mg/mL and — mg/mL, respectively. The nominal content of cholesterol in the product is 3.3 mg/mL.

3. Provide two-sided ranges for particle size distribution [
] for the drug product.

A two-sided range for d_{50} (median) is already part of the product specifications (17.0–23.0 µm). We are adding the following ranges for d_{10} and d_{90} to the product specifications:

d_{10}: [ ] µm
d_{90}: [ ] µm

4. Provide [

]

SkyePharma will [

] during the manufacture of the product. A proposal for such studies, including appropriate timeframes for conducting the studies and reporting results, will be prepared and provided to the Agency for review by June 1, 2004.

5. Provide the revised drug product specifications as recommended below:

- **"Individual drug-related unspecified and unidentified degradation products: NMT — "**
- **"Total (Sum of all reportable degradation products —):**
- **Drug release: Day 1: NLT — Day 2: — Day 3: — Day 4: NMT —**

SkyePharma has added the above specifications, and have set the specification for total reportable degradation products at NMT — (See Attachment 1.)

SkyePharma has tightened the in-vitro release specifications on an interim basis per the Agency request. (See Attachment 1.) SkyePharma plans to re-examine these specifications per the plan outlined in Item 6 below.

6. **Note that the recommended acceptance criteria for the drug release are based on the data from commercial scale batches reported in the NDA and are considered tentative in nature. Provide an agreement that the drug release specification will be revised following manufacturing experience of one year or — additional batches, whichever is earlier and that a prior-approval supplement will be submitted to this effect.**

SkyePharma agrees to revise the in-vitro release specifications following manufacturing experience of — additional batches, which should be expected to be completed in 2005, and to submit a prior-approval supplement with this additional information.

7. **Provide the revised post-approval stability protocol with the following provisions.**
   a) **Storage of the drug product in the inverted position**
   b) **Testing for the particle size distribution and [ ] content**

Please refer to the revised post-approval stability protocol provided in Attachment 2. Product will be stored in the inverted position. Testing for particle size distribution is already part of the post-approval stability protocol. A method for the determination of [ ] content will be developed and validated within the next four months and is being included in the post-approval stability protocol.

8. **Revise the statement for your post-approval stability testing commitment to include the following:**

   a. **The results of these studies will be submitted in periodic reports or upon request.**
   b. **Any lots found to fall outside the approved specifications for the drug product may be withdrawn from the market. Deviations that do not affect the safety and efficacy of the product will be promptly discussed with the reviewing division and must be reported to FDA under 21 CFR 314.81(b)(1)(ii)"**

SkyePharma hereby commits to the following with regard to the post-approval stability testing of SKY0401:

a. The results of post-approval stability studies will be submitted to the NDA in periodic reports or upon request of the Agency.
b. Any lots found to fall outside the approved specifications for the drug product may be withdrawn from the market. Deviations that do not affect the safety and efficacy of the product will be promptly discussed with the reviewing division and will be reported to FDA under 21 CFR 314.81 (b)(1)(ii).

9. **Provide an agreement to revise the drug substance specifications concurrently with the revisions made by [ ] to include a limit on [ ] impurity.**

SkyePharma agrees to revise the drug substance specifications concurrently with the revisions made by [ ] to include a limit on [ ] impurity.

SkyePharma further commits to contacting [ ] to obtain a copy of the final reports of the genotoxicity testing [ ] to assess the results, and to submit a copy of these reports to NDA 21-671.

If you have any questions regarding this submission, please contact Paula Adams, Ph.D. by telephone at (858) 625-2414 ext. 3215 or by fax at (858) 558-6617.

Sincerely,

Steven W. Jensen
Director, Regulatory Affairs

3 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21671	Efficacy Supplement Type SE-	Supplement Number NA	
Drug: DepoDur (morphine sulfate extended-release liposome injection)		Applicant: SkyePharma, Inc	
RPM: Sara Stradley		HFD-170	Phone # 827-7430
Application Type: ( ) 505(b)(1) (x) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): Duramorph, NDA 18-565	

❖ Application Classifications:	
• Review priority	(x) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	NA
❖ User Fee Goal Dates	May 18, 2004 (AP)
❖ Special programs (indicate all that apply)	(x) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(x) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (x) No
• This application is on the AIP	( ) Yes (x) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(x) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted.	(x) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.	21 CFR 314.50(i)(1)(*i*)(A) (x) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified NA

❖ Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (x) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	Filing Rev 9/24/03
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	NA
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X (as found in the AP letter)
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X (see ODS review in "labels" section)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	X
• Reviews	X (ODS-April 26, 2004)
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	X (sponsor's submission) See AP letter
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	X January 13, 2000
• Pre-NDA meeting (indicate date)	X March 26, 2003
• Pre-Approval Safety Conference (indicate date; approvals only)	NA
• Other	NA

❖ Advisory Committee Meeting	
• Date of Meeting	NA
• 48-hour alert	NA
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	NA
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	X (May 18, 2004)
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	X (May 18, 2004)
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	NA
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See medical rev
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	See ODS rev (April 20, 2004)
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet *(NME approvals only)*	NA
❖ Statistical review(s) *(indicate date for each review)*	X (April 30, 2004)
❖ Biopharmaceutical review(s) *(indicate date for each review)*	X (May 6, 2004)
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	X (April 28, 2004)
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	NA
• Bioequivalence studies	NA
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	X #1 and #2 (May 14, 2004)
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	See CMC review
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	X (April 20, and May 17, 2004)
❖ Facilities inspection (provide EER report)	Date completed: May 6, 2004 **(X)** Acceptable **( )** Withhold recommendation
❖ Methods validation	**( )** Completed **(X)** Requested **( )** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	X (May 14, and May 18, 2004)
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	NA
❖ CAC/ECAC report	NA

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/s/

Sara Stradley
5/18/04 07:39:55 PM

Stradley, Sara

From: Stradley, Sara
Sent: Thursday, May 13, 2004 6:57 PM
To: Paula Adams (E-mail)
Cc: Stradley, Sara
Subject: CMC info request

Paula
Here is a list of items that we need ASAP. Because of the short notice, it will be easier if things are emailed or if you prefer Faxed to me at 301-443-7068...I will make sure they are processed to your application. There is not going to be time to process any electronic submissions. I am working on scheduling the TC.

List of CMC Comments to NDA 21671:

1. Provide a certification from your vendor [ ] verifying that [ ]

2. Provide the LOD and LOQ for the cholesterol testing method.

3. Provide two-sided ranges for particle size distribution [ ] for the drug product.

4. [ ]

5. Provide the revised drug product specifications as recommended below:

   "Individual drug-related unspecified and unidentified degradation products: NMT [ ]
   "Total (Sum of all reportable degradation products [ ]

   Drug release: Day 1: NLT — Day 2: — Day 3: — Day 4: NMT —

6. Note that the recommended acceptance criteria for the drug release are based on the data from commercial scale batches reported in the NDA and are considered tentative in nature. Provide an agreement that the drug release specification will be revised following manufacturing experience of one year or — additional batches, whichever is earlier and that a prior-approval supplement will be submitted to this effect.

7. Provide the revised post-approval stability protocol with the following provisions.

   a) Storage of the drug product [ ]
   b) Testing for the particle size distribution and [ ]

8. Revise the statement for your post-approval stability testing commitment to include the following:

   a. The results of these studies will be submitted in periodic reports or upon request.
   b. Any lots found to fall outside the approved specifications for the drug product may be withdrawn from the market. Deviations that do not affect the safety and efficacy of the product will be promptly discussed with the reviewing division and must be reported to FDA under 21 CFR 314.81(b)(1)(ii)"

9. Provide an agreement to revise the drug substance specifications concurrently with the revisions made by [ ] to include a limit on [ ] impurity.

Sara Stradley
Regulatory Project Manager
Division of Anesthetics, Critical Care
and Addiction Drug Products
301-827-7430

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/s/

Sara Stradley
5/14/04 09:39:25 AM
CSO

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_____ § 552(b)(5) Draft Labeling

5-6-04

MEMORANDUM OF TELECON

DATE: May 5, 2004

APPLICATION NUMBER: NDA 21-671

BETWEEN:

Name: [redacted] Consultant Toxicologist
Steven W. Jensen, Director, Regulatory Affairs
Paula Adams, PhD, Assoc. Director, Regulatory Affairs
Phone: 1-800-930-9002, code 8372233
Representing: SkyePharma Inc

AND

Name: Dan Mellon, PhD, Supervisor, Pharmacology/Toxicology
Mamata De, PhD, Pharmacology/Toxicology Reviewer
Sara Stradley, MS, Regulatory Project Manager
Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170

SUBJECT: [redacted]

Dr. Mellon informed the Sponsor that [redacted] has been identified in certain classes of opioids. This structure is believed to be an impurity from the [redacted] Dr. Mellon advised the Sponsor to contact their DMF holder and request that the DMF holder determine if any impurities containing [redacted] are present in their product.

The Sponsor agreed to contact their DMF holder and, if such an impurity is identified, notify the Division.

Drafted by: SES May 6, 2004
Initialed by: reviewed by Dan Mellon May 7, 2004
TELECON

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/s/

Sara Stradley
5/7/04 08:32:58 AM
CSO

CONSULTATION RESPONSE
Division of Medication Errors and Technical Support
Office of Drug Safety
(DMETS; HFD-420)

DATE RECEIVED:	**DESIRED COMPLETION DATE:** March 26, 2004	**ODS CONSULT #'s:**
February 9, 2004	**PDUFA DATE:** May 18, 2004	04-0037 and 03-0279

TO: Bob Rappaport, M.D.
Director, Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

THROUGH: Sara E. Stradley
Project Manager, Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

PRODUCT NAME:	**NDA SPONSOR:**
[redacted] and Depodur (alternate) (Morphine Sulfate [redacted] Liposome Injection) 10 mg/mL **NDA#:** 21-671	SkyePharma Inc.

SAFETY EVALUATOR: Scott Dallas, R.Ph.

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name [redacted] but has no objections to the use of the proprietary name Depodur. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review to minimize potential errors with the use of this product.

3. DMETS recommends that the Division request the sponsors of the non-modified morphine sulfate injections make labeling revisions to prevent its confusion with this new morphine sulfate [redacted] liposome injection. These changes should be requested at the time of approval of this application. DMETS recommends that the Division coordinate requests for revisions with the Office of Generic Drugs such that generic morphine sulfate injection labeling can be updated at the same time.

4. DDMAC finds the proprietary names [redacted] and Depodur acceptable from a promotional perspective.

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax (301) 443-9664

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Building Room 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: March 23, 2004

NDA NUMBER: 21-671

NAME OF PRODUCT: [redacted] and Depodur (alternate)
(Morphine Sulfate Sustained Release Liposome Injection)
10 mg/mL

NDA SPONSOR: SkyePharma Inc.

*** NOTE: This review contains proprietary and confidential information that should not be released to the public. ****

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthetic, Critical Care and Addiction Drug Products for an assessment of the proposed proprietary names, [redacted] and Depodur. Draft container labels, carton and insert labeling were provided for review and comment.

The Office of Drug Safety (ODS) has also reviewed the proposed risk management plan for this product. Comments concerning the risk management plan have been forwarded in a separate memorandum to the review division (HFD-170).

PRODUCT INFORMATION

[redacted] Depodur is an extended release liposome injection of morphine sulfate indicated for the treatment of post-operative pain. The medication is administered by the epidural route, at the lumbar or lower thoracic levels, and administered prior to surgery or after clamping the umbilical cord during a cesarean section. The medication is not intended for the intrathecal, intravenous or intramuscular routes of administration. The product is available as a preservative-free morphine sulfate extended release liposome injection in a concentration of 10 mg/mL.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1, 2] as well as several FDA databases[3] for existing drug names

[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, 2004, Facts and Comparisons, St. Louis, MO.
[3] The Drug Product Reference File [DPR], the DMETS database of proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

which sound-alike or look-alike to [redacted] and Depodur to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system (TESS) was conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted prescription analysis studies, involving health care practitioners within FDA. These exercises were conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the names.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names [redacted] and Depodur. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary names [redacted] and Depodur acceptable from a promotional perspective.

2. The Expert Panel identified two proprietary names that were thought to have the potential for confusion with [redacted] These products are listed in Table 1 (see page 4), along with the dosage form available and usual dosage.

3. The Expert Panel did not identify any proprietary names that were thought to have the potential for confusion with "Depodur".

[4] Website location http://tess2.uspto.gov/bin/gate.exe?f=tess&state=7cljht.1.1
[5] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s) and Strength(s)	Usual adult dose*	Other**
[ ]	Morphine Sulfate Sustained-Release Liposome, Injection, 10 mg/mL	Inject 10 mg to 20 mg epidurally one time. Dose depends upon the type of surgery and age of the patient.	
Morphine Sulfate	Morphine Sulfate, Injection, 1 mg/mL, 2 mg/mL, 4 mg/ml, 5mg/ml, 8 mg/ml, 10 mg/mL, 15 mg/mL, 25 mg/mL, 50 mg/mL, also available in: Tablets; Tablets, Extended-Release; Tablets, Soluble; Capsules, Extended- Release; Solution, Oral; and Suppositories, Rectal	Routes of administration for the injectable dosage formulation are subcutaneous, intramuscular, intravenous, intrathecal and epidural. Epidural administration: Initially inject 5 mg in the lumbar region. May increase incrementally with 1 mg to 2 mg doses up to a maximum of 10 mg/24 hours.	SA/LA
Depo-Medrol	Methylprednisolone Acetate, Injection, 20 mg/mL, 40 mg/mL, and 80 mg/mL	Routes of administration are intramuscular, intra-articular and intralesional. Inject intramuscularly 40mg to 120 mg weekly depending upon the condition.	LA
[		]	SA
[		]	

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)
***Name pending approval. Not FOI releasable.

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. The Expert Panel (EPD) discussed all names considered to have significant phonetic or orthographic similarities to [ ] and Depodur. A search of POCA did not identify any additional names of concern that were not discussed in EPD.

D. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Six separate studies were conducted within the Centers of the FDA for the proposed proprietary names to determine the degree of confusion of [ ] and "Depodur" with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 124 health care professionals (pharmacists, physicians, and nurses) for each proposed proprietary name. These exercises were conducted in an attempt to simulate the prescription ordering process. Two inpatient orders were written, each consisting of a combination of marketed and unapproved drug products and a prescription for [ ] or "Depodur". These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via email. In addition, inpatient orders were recorded on voice mail and included an order for [ ] or "Depodur". The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

a. [ ] Prescriptions:

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Intpatient Sample 1: [ ]	*Inpatient Verbal Order:* [ ] 10 mg by epidural times one
Inpatient Sample 2: [ ] 10mg by epidural x1	

b. Depodur Prescriptions:

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Intpatient Sample 1: [illegible]	*Inpatient Verbal Order:* Decrease the Depodur to 10 mg epidurally for one more dose
Inpatient Sample 2: Decrease Depodur to 10mg Epidurally for 1 more dose	

2. Results:

a. [ ]

One participant in the verbal prescription study interpreted the proposed name as [ ] is the established name for an unapproved medication. See Attachment A for the complete listing of interpretations from the verbal and written prescription studies.

b. Depodur

One participant commented that several injectables start with "Depo", and "it's probably safer not to use that again." A second participant commented that Depodur is "too similar to Theo-dur". See Attachment B for the complete listing of interpretations from the verbal and written prescription studies.

E. SAFETY EVALUATOR RISK ASSESSMENT

1. Look-alike and Sound-alike Concerns with [ ]

In reviewing the proposed proprietary name '[ ]", the primary concerns related to the potential for look-alike and sound-alike confusion with [ ] Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that the proposed name, [ ] could be confused with [ ] One respondent from the verbal prescription study misinterpreted the name, [ ] for an established name, [ ], of an unapproved drug product. Although there are limitations to the predictive value of these studies, primarily due to sample size, we have acquired safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

a. [

1 Page(s) Withheld

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2. Look-alike and Sound-alike Concerns with Depodur

In reviewing the proposed proprietary name "Depodur", the expert panel discussions and independent analysis did not identify any proprietary names with the potential for look-alike and sound-alike confusion with Depodur. Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name, DepoDur, could be confused with other established or proprietary names. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Depodur. However, negative findings are not predictive as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. Two participants in the prescription studies did include comments concerning the proposed name. One participant commented that several injectables start with "Depo", and "it's probably safer not to use that again." The second participant commented that Depodur is "too similar to Theo-dur".

Safety concerns involving the use of "Depo" as part of the proprietary name are discussed further in subsection 3, titled "The prefix "Depo" – Possible Administration Confusion".

Theo-dur was the proprietary name for a theophylline extended release tablet. However, this product is no longer available in the U.S. market place. An on-line search conducted of the electronic Physicians Desk Reference, Drug Facts & Comparison, Orange Book, and the United States Patent and Trademark Office database indicated that the proprietary name was not listed in these reference sources. Also the proprietary name, Theo-dur, was not cross-referenced during a search of two on-line consumer websites, drugstore.com and destinationrx.com. However, the proprietary name, Theo-dur, is known by older healthcare professionals and is listed in the on-line version of the Micromedex Integrated Index. Based on the limited use of the proprietary name, Theo-dur, the risk should be minimal for confusion between the proprietary name Theo-dur or a generic theophylline product and the proposed product, morphine sulfate sustained-release liposome injection.