CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208603Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DATE: March 7, 2017

TO: ARYMO ER (morphine sulfate extended-release tablets) (NDA 208603) File
CDER Orange Book Staff

FROM: CDER Exclusivity Board

SUBJECT: Addendum to Exclusivity Summary for NDA 208603 (Jan. 9, 2017)

NDA 208603 for ARYMO ER (morphine sulfate extended-release tablets) was approved on January 9, 2017. At the time of approval, a completed Exclusivity Summary dated January 4, 2017 ("original Exclusivity Summary"), was made part of the administrative record for NDA 208603.

The CDER Exclusivity Board, in conjunction with the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) in CDER, continues to review and assess responses to certain questions in the original Exclusivity Summary. Any modifications to these responses, if necessary, will be made in a revised Exclusivity Summary that supersedes the original Exclusivity Summary.

Sanjay Sitlani -S

Digitally signed by Sanjay Sitlani -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sanjay Sitlani -S, 0.9.2342.19200300.100.1.1=2000359378
Date: 2017.03.08 15:03:38 -05'00'

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

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/s/

CHRISTOPHER M HILFIGER
03/09/2017

SHARON H HERTZ
03/09/2017

EXCLUSIVITY SUMMARY

NDA # 208603 SUPPL # HFD # 170

Trade Name ARYMO ER

Generic Name morphine sulfate extended-release tablets

Applicant Name EGALET CORP

Approval Date, If Known January 9, 2017

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 questions about the submission.

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

YES ☒ NO ☐

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

505(b)(2)

b) 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 ☒ 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.

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:

c) Did the applicant request exclusivity?

YES ☐ NO ☒

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

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

YES ☐ NO ☒

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 ☒

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 ☐

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

NDA# 206544 MorphaBond

NDA# 019516 MS Contin

NDA# 020616 Kadian

NDA# 021260 Avinza

NDA# 019977 Oramorph SR

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 ☒

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 NDAs 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 ☒ 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 ☒ 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 ☐

(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 ☒

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 ☐

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 Randomized, Double-Blind, Double-Dummy, Active and Placebo-Controlled, Crossover Study Comparing the Abuse Potential of Manipulated and Manipulated/Sieved Egalet® PR Morphine Tablets versus Manipulated MS CONTIN following Intranasal Administration in Nondependent Recreational Opioid Users

The results of this study cannot be included in the labelling due to the exclusivity held by Morphabond (NDA 206544).

A Randomized, Double-Blind, Triple-Dummy, Active and Placebo-Controlled, Four-Way Crossover Study with an Exploratory Fifth Arm Comparing the Abuse Potential of Manipulated and Intact Egalet® PR Morphine Tablets versus Manipulated MS CONTIN Following Oral Administration in Nondependent Recreational Opioid Users

This is a failed study, but was included in labeling based on our current approach to reporting studies of abuse-deterrent properties, whether positive or negative.

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 ☐

Investigation #2 YES ☐ NO ☐

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

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 ☒

Investigation #2 YES ☐ NO ☐

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

n/a

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"):

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 !
!
IND # 117317 YES ☒ ! NO ☐
! Explain:

(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 ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! 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 ☒

If yes, explain:

==========

Name of person completing form: Christopher Hilfiger
Title: Regulatory Health Project Manager
Date: 1/4/17

Name of Division Director signing form: Sharon Hertz, MD
Title: Director, DAAAP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/

CHRISTOPHER M HILFIGER
01/09/2017

SHARON H HERTZ
01/09/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208603 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Arymo Established/Proper Name: Morphine Sulfate Dosage Form: Tablet		Applicant: Egalet Agent for Applicant (if applicable):
RPM: Christopher Hilfiger		Division: DAAAP

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☒ New patent/exclusivity *(notify CDER OND IO)*
Date of check: 12/19/16

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is October 15, 2016	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☒ MedGuide
☒ Communication Plan
☒ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☒ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 01/09/17
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	3/4/16 2/29/16
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ None DMEPA: ☐ None 3/11/16, 3/30/16 DMPP/PLT (DRISK): ☐ None 10/11/16 OPDP: ☐ None 10/7/2016 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☐ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	01/09/17 ☐ Not a (b)(2) 10/3/16
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP
  ○ If yes, Center Director's Exception for Review memo *(indicate date)*
  ○ If yes, OC clearance for approval *(indicate date of clearance communication)*
	☐ Yes ☒ No
	
	☐ Not an AP action

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: Arymo is not a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, IDT is exempt from the requirement for an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients under the Pediatric Research Equity Act (PREA) (21 USC 355c).	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Included
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 08/14/15
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 08/27/14
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	

❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	08/04/16
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 01/09/17
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 10/02/16
PMR/PMC Development Templates *(indicate total number)*	☐ None 18
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	09/23/16
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	09/23/16 – clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☐ N/A 08/15/16
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	10/5/16 01/06/17 ☐ None 10/13/16
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 07/11/2016
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 09/09/16
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 10/04/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None 09/27/16 Drug Substance 9/7/16 Drug Product 9/27/16 Category I Studies 9/19/16 Process (includes microbiology) 9/12/16 Facilities 9/7/16 Biopharmaceutics 9/15/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	9/27/16 in Drug Product Review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable 09/07/16 Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☒ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

SELMA S KRAFT
02/23/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208603

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Egalet US Inc.
460 E. Swedesford Rd.
Suite 1050
Wayne, PA 19087

ATTENTION: Michele Roy RN, MS
Executive Director, Regulatory Affairs

Dear Ms. Roy:

Please refer to your New Drug Application (NDA) dated and received December 14, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Morphine Sulfate Extended-release Tablets, 15 mg, 30 mg and 60 mg.

We also refer to your correspondence, dated and received December 31, 2015, requesting review of your proposed proprietary name, Arymo ER.

We have completed our review of the proposed proprietary name, Arymo ER and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your December 31, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Wendy Brown, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-9140. For any other information regarding this application, contact Christopher M. Hilfiger, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4131.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
03/04/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208603

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Egalet US, Inc.
460 E. Swedesford Road
Suite 1050
Wayne, PA 19087

Attention: Michele Roy RN, MS
Executive Director, Regulatory Affairs

Dear Ms. Roy:

Please refer to your New Drug Application (NDA) dated December 14, 2015, received December 14, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for ARYMO ER (morphine sulfate) extended-release tablets, 15 mg, 30 mg, and 60 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 14, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 24, 2016.

We are currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. Provide additional information about the manufacturing development and the physical properties of the morphine sulfate drug substance used to prepare the drug product registration batches. For example, (b) (4) .

   a. (b) (4)

   b. (b) (4) Include the rationale or data used to support this determination.

   c. (b) (4)

      i. (b) (4)

      ii. (b) (4)

      iii. (b) (4)

2. Provide data from a swelling study in water and gastric fluid demonstrating the size of the tablet over time. Provide data that includes photos and dimensions of the tablet as it swells in the fluid.

3. Clarify how many units were used for dissolution tests for each batch in batch analyses listed under Module 3.2.P.5.4. Provide the complete dissolution profile data including the individual, mean, standard deviation and profiles for the batch analyses data of the following batches: 15 mg (SB69400101, SB69400201, and SB69400301), 30 mg (SB69200101, SB69200201, and SB69200301), 60 mg (SB69300101, SB69300201, and SB69300301), 60 mg used in study 067-EG-001 (13-0002-067, 13-0003-067, and 13-0004-067), 60 mg used in 067-EG-002 (13-0033-067, 13-0034-067, 13-0050-067, and 13-0051-067), and 100 mg used in study 067-EG-004 and 067-EG-005 (SB69500101). Submit the in vitro in vivo correlation (IVIVC) project file in Phoenix Wizard Platform (WinNonlin project file (*.*phxproj) for study 067-EG-002.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient

PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Christopher Hilfiger, Regulatory Project Manager, at (301) 796-4131.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Division Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

SHARON H HERTZ
02/24/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208603

NDA ACKNOWLEDGMENT

Egalet US, Inc.
460 E. Swedesford Road
Suite 1050
Wayne, PA 19087

Attention: Michele Roy RN, MS
Executive Director, Regulatory Affairs

Dear Ms. Roy:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: ARYMO ER (morphine sulfate) extended-release tablets, 15 mg, 30 mg, 60 mg

Date of Application: December 14, 2015

Date of Receipt: December 14, 2015

Our Reference Number: NDA 208603

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 12, 2016, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labelling must conform to the content and format requirements of revise 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me, at (301) 796-4131.

Sincerely,

{See appended electronic signature page}

Christopher Hilfiger
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

CHRISTOPHER M HILFIGER
12/17/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 117317

MEETING MINUTES

Egalet Ltd.
460 E Swedesford Road
Suite 1050
Wayne, PA 19807

Attention: Jeffrey M. Dayno, MD
Chief Medical Officer

Dear Dr. Dayno:

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for morphine PR (EG-001) Tablets.

We also refer to the telecon between representatives of your firm and the FDA on August 14, 2015. The purpose of the meeting was to discuss your NDA submission.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4131.

Sincerely,

{See appended electronic signature page}

Christopher Hilfiger
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: pre-NDA

Meeting Date and Time: August 14, 2015, at 10:00 AM
Meeting Location: Teleconference

Application Number: IND 117317
Product Name: morphine PR (EG-001)
Indication: for the management (b) (4) pain (b) (4)

Sponsor/Applicant Name: Egalet Ltd.

Meeting Chair: John Feeney, MD
Meeting Recorder: Christopher Hilfiger

FDA ATTENDEES

Sharon Hertz, MD	Division Director
John Feeney, MD	Clinical Team Leader
Tim Jiang, MD	Medical Officer
Dan Mellon, PhD	Non-Clinical Supervisor
Elizabeth Bolan, PhD	Non-Clinical Reviewer
Yun Xu	Clinical Pharmacology Supervisor
James Tolliver, PhD	Controlled Substance Staff Reviewer

SPONSOR ATTENDEES

Jeffrey M. Dayno, MD	Chief Medical Officer
John Lawler	Executive Director, Clinical Operations
Robert Radie	President and Chief Executive Officer
Michele A. Roy RN, MS	Executive Director, Regulatory Affairs
Gwendolyn Niebler, DO, MBA	Senior Vice-President, Clinical Development and Medical Affairs

BACKGROUND

The goal of this meeting was to reach an agreement on certain aspects of the NDA submission for morphine PR which will be submitted pursuant to Section 505(b)(2) of the Federal Food,

Drug, and Cosmetic Act. This product will be an abuse-deterrent formulation of extended-release morphine sulfate.

FDA sent Preliminary Comments to Egalet Ltd. on August 10, 2015. Egalet Ltd. sent responses to the Division's preliminary comments on August 12, 2015 (Appendix A).

DISCUSSION

Question 1.

(b) (4)

Does the Agency concur with this approach?

FDA Response:

No, we disagree. As we commented at the End-of-Phase 2 meeting, you should have both an ISE and an ISS which should include comprehensive discussions of how your application plans to rely on the Agency's findings for the listed drugs as well as any cited literature references to support an overall finding of efficacy and safety for this product.

Egalet response:

Egalet agrees and acknowledges that an NDA submission must be a complete NDA, which requires an ISE and an ISS. Acknowledging that clinical efficacy studies were not required and therefore not conducted for this program, Egalet intends to provide the text portion of the ISE, which will also function as the SCE in Module 2. As such, the ISE will include a comprehensive discussion of how the application relies on the Agency's findings of efficacy for the listed drug, MS Contin.

The application will include results of an extensive search of the literature to identify studies that support the efficacy and safety profile that has been well established for extended release morphine. Based on pre-specified inclusion and exclusion criteria, pertinent studies will be sorted and presented in order of relevance, as well as summarized in a table that provides key study attributes. Based on these studies, Egalet will include a comprehensive discussion

regarding the evidence of effectiveness from the literature and how the application relies on the Agency's findings for the listed drug.

Discussion:

The Division found the approach outlined in the Egalet response acceptable.

Question 2.

As referenced in FDA's Guidance for Industry, Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document, Egalet plans to submit a Section 2.7.4, Summary of Clinical Safety (SCS), which will be sufficiently detailed to serve as the narrative portion of the ISS in Module 5 while still concise enough to meet the requirements for Module 2.

In addition, for the Integrated Summary of Safety (ISS) tables, appendices, and datasets in Module 5, Section 5.3.5.3 (Reports of Analyses of Data from more than One Study), Egalet plans to provide two integrated sets of summary tables with datasets, one from the combined pivotal bioequivalence studies and one from the combined human abuse liability studies.

Does the Agency concur with this approach?

FDA Response:

See response to Question 1.

Separate integrated sets of summary tables with datasets, one from the combined pivotal bioequivalence studies, and one from the combined human abuse liability studies is acceptable. All adverse events encountered during the clinical development program and associated with potential abuse, misuse, overdose, diversion, and tampering should be documented. Case narratives of each of these adverse events should be provided. For additional details regarding the documentation of AEs consult the January 2010 FDA Guidance for Industry: Assessment of Abuse Potential of Drugs document available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

Egalet response:

Egalet intends to use the same approach for the ISS as described for the ISE. In addition, based on safety data obtained from the clinical program, Egalet will provide integrated sets of summary tables with datasets, as proposed in our pre-NDA briefing document, which the Division found to be acceptable.

Discussion:

The Division found the approach outlined in the Egalet response acceptable.

Question 3.

Egalet intends to request a priority review designation for the EG-001 NDA.

Does the Agency concur that this NDA qualifies for priority review?

FDA Response:

To qualify for a priority review, your product must address an unmet medical need in the treatment of a serious condition. Since there is already an approved abuse-deterrent morphine product, your product will only qualify for priority review if you perform comparative studies to demonstrate that your product is safer or more efficacious than existing products.

Egalet response:

Egalet acknowledges and appreciates the Division's preliminary comments regarding our intent to request Priority Review for EG-001. We also acknowledge the existence of an approved abuse-deterrent (AD) morphine product – Embeda (morphine sulfate and naltrexone hydrochloride) – that was originally approved in August 2009 but not available between 2011 and Oct-2014, during which time it was not on the market (b) (4) ***The serious and important public health issue regarding opioid misuse, abuse, addiction, overdose and death is well recognized. Because of this, one of the FDA's stated priorities is to work with Sponsors to approve and make available additional abuse-deterrent formulations of opioid medications (based on new technologies) in the spirit of "incremental improvement". Egalet proposes that EG-001 fulfills an unmet medical need in the class of abuse-deterrent extended-release morphine products by being the first product with a physical/chemical barrier approach to abuse deterrence, and that this formulation also offers a safer profile than Embeda, without the risks of opioid withdrawal and alcohol dose dumping.***

EG-001, which is formulated utilizing Egalet's proprietary technology that employs plastic injection molding as part of its manufacturing process, represents a novel approach to abuse deterrence compared to Embeda. This is based on EG-001's physical and chemical barrier features that resist both common and more rigorous methods of manipulation. In contrast to this, Embeda employs an agonist/antagonist combination approach to abuse deterrence. However, this approach introduces an additional pharmacologic agent in the formulation which, whether inadvertently misused (e.g., chewed) by an appropriate patient or purposely abused for nonmedical purposes, poses the risk of opioid withdrawal in individuals who are opioid- dependent.

An additional safety risk with Embeda is its interaction with alcohol. The Prescribing Information contains a Black Box Warning on Interaction with Alcohol to warn HCPs and patients that co-ingestion of alcohol with Embeda may result in an increase of plasma levels and potentially fatal overdose of morphine. Our NDA submission will provide an in vitro alcohol interaction study, which demonstrated no evidence of alcohol dose dumping for EG-001 in the presence of increasing concentrations of alcohol (up to 40%).

Therefore, as compared to the currently approved abuse-deterrent morphine product, Egalet proposes that the product profile of EG-001 is different and has features that will represent an improved safety profile. This, along with EG-001's novel and differentiated mechanism of abuse-deterrence, which represents the first physical/chemical barrier extended-release morphine product candidate, addresses an unmet medical need, which could help to reduce the burden of opioid misuse, abuse, addiction, overdose and death. Egalet requests the Division's consideration of these points during their initial review period for granting Priority Review of our EG-001 NDA.

Discussion:

The Sponsor stated that EG-001 has a more favorable profile than the existing morphine sulfate abuse-deterrent product, EMBEDA, because dose dumping in alcohol is not observed with EG-001. The Division replied that the Sponsor's argument will be considered in deciding whether to grant a priority review for the New Drug Application (NDA). The Sponsor's argument will be discussed internally at the time of NDA submission and a decision (Standard or Priority) will be made when the NDA is filed.

The Division asked the Sponsor the anticipated submission date for their NDA. The Sponsor stated that they intend to submit their NDA prior to the end of this calendar year. The Division reminded the Sponsor that they should be available to respond to any information requests the Division may have during the 60-day filing period. The Sponsor agreed.

Additional clinical comment:

In your briefing package, you stated "the safety profile of EG-001 will be based on a minimum of 100 subjects." We remind you that the 100 subjects must be treated with the "to-be-marketed formulation" via the oral route.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.
Because none of the criteria apply at this time to your application, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's

interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 117317

MEETING MINUTES

Egalet Ltd.
460 E Swedesford Road
Suite 1050
Wayne, PA 19807

Attention: Carol S. Marchione
Regulatory Affairs Representative for Egalet

Dear Ms. Marchione:

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for morphine PR (EG-001) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on August 27, 2014. The purpose of the meeting was to discuss your clinical, chemistry, manufacturing, and controls (CMC), and regulatory questions associated with your planned NDA submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4131.

Sincerely,

{See appended electronic signature page}

Christopher Hilfiger
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	August 27, 2014, at 3:00 PM
Meeting Location:	FDA White Oak Campus
Application Number:	IND 117317
Product Name:	Morphine PR
Indication:	for the management of (b) (4) pain (b) (4)
Sponsor/Applicant Name:	Egalet, Ltd
Meeting Chair:	John Feeney, MD
Meeting Recorder:	Christopher Hilfiger

FDA ATTENDEES

Sharon Hertz, MD	Deputy Division Director
John Feeney, MD	Clinical Team Leader
Timothy Jiang, MD, PhD	Medical Officer
Elizabeth Bolan, PhD	Non-Clinical Reviewer
Dan Mellon, PhD	Non-Clinical Supervisor
Eric Duffy, PhD	Director, Division of New Drug Quality Assessment II
Julia Pinto, PhD	ONDQA Branch Chief
Xiaobin Shen, PhD	CMC Reviewer
Janice Derr, PhD	Statistical Team Leader
Katherine Meaker, PhD	Statistical Reviewer
Yun Xu, PhD	Clinical Pharmacology Supervisor
Srikanth Nallani, PhD	Clinical Pharmacology Reviewer

SPONSOR ATTENDEES

Ryan Daufenbach	Executive Director, Head of Marketing
Torben Elhauge, MSc	Director, Analytical Development
John Lawler	Sr. Director, Clinical Operations
Karsten Lindhardt	MSc, PhD, Senior VP, Head of R&D
Jeffrey M. Dayno, MD	Clinical Consultant
Carol S. Marchione	Marchione & Associates LLC, Regulatory Consultant

(b) (4)	Consultant
Lynn Webster, MD	Consultant
(b) (4)	Consultant

BACKGROUND

The purpose of this meeting is to discuss the clinical, chemistry, manufacturing, and controls (CMC), and regulatory questions associated with the planned NDA submission for Egalet®-001 (morphine PR) Tablets. Egalet®-001 (morphine PR) Tablets will be submitted under the 505(b)(2) regulatory pathway referencing NDA 19516 for MS CONTIN®(morphine sulfate extended-release tablets). The Division provided the Sponsor Written Responses to their pre-IND questions on March 2, 2013. The Sponsor submitted the original IND on August 22, 2013. A Fast Track designation was granted for this IND on February 18, 2014. The Sponsor completed their Tier 1 abuse-deterrent studies and is seeking input on Tier 2 and Category 3 abuse-deterrent testing protocols. Additionally, the Sponsor's objectives include obtaining input and agreement with the Division on the contents of an NDA submission.

DISCUSSION

Note: Your questions are reproduced below in *italicized* text. Agency responses follow each question in **bold** text. Any discussion of the questions and responses appears in normal text.

Clinical

Question 1.

Does the Agency concur that the patient exposure of Egalet®-001 (morphine PR) tablets adequately addresses the FDA guidance previously provided and therefore satisfies requirements for registration?

FDA Response:

Yes. If your product is bioequivalent to the reference drug, we agree.

Discussion:

There was no discussion of this question.

Question 2.
Does the Agency concur that results from the Category 1 abuse deterrent studies conducted with Egalet®-001 (morphine PR) tablets, along with the studies being proposed, are acceptable to evaluate the limits of the abuse deterrent properties of Egalet's proprietary technology?

FDA Response:

No. We do not agree [redacted] (b) (4) (b) (4)

Based on review of the available information, we are providing comments on the Category 1 Phase 1 and Phase 2 studies, synopsis for PK study protocol 067-EG-010, and for the revised protocol for oral human abuse potential study 067-EG-008.

The following comments pertain to Category 1, Phase 1 and Phase 2, studies on Egalet morphine PR tablets.

1. **Preliminary examination of the Category 1, Phase 1 and Phase 2 study reports reveal that a variety of in vitro physical manipulation and chemical extraction studies under various conditions were conducted on Egalet morphine PR tablets and the comparator. Detailed evaluation of these Category 1 studies as part of the overall assessment of abuse-deterrent properties for Egalet morphine PR tablets will have to await submission under an NDA.**

2. **Category 1 studies to be submitted in support of an NDA must be conducted on the to-be-marketed formulation. Document whether or not the in vitro studies described in your Category 1, Phase 1 and Phase 2 study reports were conducted on the to-be-marketed formulation. In addition, provide information on the batch numbers of the product used in these studies.**

3. **Examine the effect of cutting Egalet tablets into numerous small pieces followed by grinding the pieces with a mortar and pestle on particle size.**

4. **Conduct a study using standard dissolutions techniques to examine the release of morphine sulfate from Egalet morphine PR tablets that are cut into a variety of pieces such as 2, 4, 8, 16, and 32 pieces, as well as ground. Such a study would mimic the direct ingestion of cut tablets by individuals either abusing or misusing Egalet morphine PR tablets by cutting.**

5. **Include the number of replicates used in extraction studies using various solvents in your Category 1, Phase 2 study report. We recommend that you conduct Category 1 studies using at least 3 or more replicates.**

6. **Provide an explanation for** [redacted] (b) (4)

7. **The descriptions provided in the Category 1, Phase 1 and 2 study reports are not clear regarding the various volumes used in the extraction studies. Include solvent volumes from the various extraction studies.**

8. **Provide a more detailed description and rationale for the use of quartered tablets and "sliced" tablets in your extraction studies.**

9. **Provide a discussion regarding changes in viscosity of the various extraction solutions resulting from use of different solvents.**

10. **Provide any information available regarding the solubility of morphine sulfate and morphine base in various solvents.**

[redacted] (b) (4)

The following comments pertain to oral human abuse potential study 067-EG-008.

1. **In order to more effectively review and provide comments regarding Protocol O67-EG-008, submit a copy of the pharmacy manual and the statistical analysis plan (SAP). If the SAP is not finalized, then at least prior to unlocking the dataset, provide a copy of the final SAP for review and comment.**

2. **The study must be conducted using the to-be-marketed formulation. Provide batch numbers for the product used in the study.**

3. **Document instances of emesis at any time during the Treatment Phase.**

4. **Provide detailed information on the manipulations to be conducted on Egalet PR morphine tablets and MS CONTIN.**

5. **Provide information on the methods of administration of each treatment. Consider evaluating two oral treatments of manipulated Egalet PR morphine, one manipulated Egalet PR morphine added to 240 mL of water, the second**

manipulated Egalet PR morphine tablet placed in the oral cavity followed by ingestion of water.

Prior to the discussion of this question and response, the Sponsor presented a slide show on the abuse-deterrent characteristics of their product. This slide show is attached as Appendix 1.

Discussion:

The Division asked whether the Sponsor had attempted multiple methods of manipulation, such as, a grinder followed by mortar and pestle. The Sponsor responded that they had not, however, will do so in the future. The Division asked the Sponsor to clarify the result of freezing the product. The Division stated that a cut time of (b) (4) seconds for manipulation is too short as drug abusers will attempt to manipulate the product for a longer time period. The Sponsor responded that they will incorporate these recommendations into further studies.

The Division noted that when the Sponsor tried to pulverize the tablets with mortar and pestle, they could study the effect of freezing the crushed coarse particles to see if the particles will become more brittle, making further particle size reduction easier. The Sponsor explained that (b) (4) (b) (4). The Division stated that such relevant and systematically studied data should be provided and asked the Sponsor to explore further reducing the particle size of manipulated cut pieces of formulation using a mortar and pestle.

The Division asked if the Sponsor had (b) (4) PK data for the manipulated products. The Sponsor stated that they do have PK data but that the product was swallowed, (b) (4) from the back of the throat. The Sponsor also stated that the manipulated particles retain the controlled-released properties but at a different dissolution rate due to the change in surface area. (b) (4)

The Sponsor stated that in their oral human abuse liability (HAL) study, both the whole product and powdered or manipulated product become sticky when placed in water. The Division asked the Sponsor to submit a video to demonstrate the effects of water on whole and manipulated product. The Division asked if there is an issue with swallowing Egalet-001 when taken with water. The Sponsor responded that there were no issues swallowing Egalet-001 with the coating (b) (4)

The Division suggested a dissolution study where the product is cut to sizes ranging from one-half the original size through one-thirty second i.e. ½, ¼, 1/8, 1/16, 1/32. The Division also recommended an oral HAL study of drug product as a powder with water.

(b) (4)

(b) (4)

Regulatory

Question 3.

Does the Agency concur with the proposed strategy in support of the REMS?

FDA Response:

We are aware that you are a member of the RPC (REMS Program committee). If approved, this application will have a slightly modified ER/LA REMS which incorporates your product specific information. It is our hope that the RPC will provide the most recently approved ER/LA REMS documents for you to revise. Otherwise, base your revised REMS documents on the most recently approved ER/LA REMS materials on the FDA REMS website.

Discussion:

There was no discussion of this question.

Question 4.

Does the Agency concur with the strategy to address the required NDA documents, understanding that safety and efficacy studies were not conducted as allowed by a 505(b)(2) application?

FDA Response:

No, we do not concur. For a 505(b)(2) NDA (b) (4) **You may only rely upon the Agency's previous finding of safety and efficacy for the referenced drug product, as reflected in the product labeling.**

For a 505(b)(2) NDA that references the Agency's previous finding of safety and efficacy for MS Contin, no pharmacology or toxicology studies would be required to support the safety of the morphine sulfate in your drug product. However, any excipient, impurity or degradant that exceeds acceptable levels will require adequate safety qualification.

Please keep in mind that for an extended-release morphine drug product, we have established a maximum theoretical daily dose (MTDD) of 2 grams of morphine/day. The justification of the safety of your excipients, as well as acceptable levels of

impurities/degradants in the drug substance and drug product as per ICH Q3A(R2) and ICH Q3B(R2) should be based on this maximum dose. Refer to Guidance for Industry: *Q3A Impurities in New Drug Substances* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf

and

Guidance for Industry: *Q3B (R2) Impurities in New Drug Products* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf

(b) (4)

(b) (4)

Does the Agency concur with this approach?

FDA Response:

No. For a 505(b)(2) NDA, (b) (4) **You may only rely upon the Agency's previous finding of safety and efficacy for the referenced drug product, as reflected in the product labeling. In addition to the summaries described above, provide both an ISE and an ISS which include a discussion of how you plan to rely on the Agency's prior findings for the referenced listed drug, along with any cited literature references that support a finding of efficacy and safety for your product.**

...Due to the nature of the clinical studies contained in the NDA described above, serious adverse events are not expected; however, if they were to occur, the only completed case report forms that will be provided will be for patients who experienced a serious adverse event, for patients who died or for patients who discontinued due to a serious adverse event. Does the Agency concur with this approach?

FDA Response:

Your proposal represents the standard requirement for Case Report Forms.

Discussion:

There was no discussion of this question.

Question 5.

Does the Agency concur that Egalet's proposal to address PREA requirements is adequate?

FDA Response:

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement. However, submit a document to the NDA stating that PREA is not applicable to your product because it does not represent a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

Discussion:

There was no discussion of this question.

Chemistry, Manufacturing, and Controls (CMC)

Question 6.

Does the Agency concur that the strategy for filing the drug product stability data meets the requirements for NDA approval?

FDA Response:

A minimum of 12 months of real time stability data from the registration batches is required at the time of the submission of the NDA.

Discussion:

(b) (4)

(b) (4) The Division encouraged the Sponsor to submit a complete application with the full 12 months of stability data to ensure that a reasonable expiry could be granted.

Question 7.

Does the Agency concur that the known impurity, [redacted] (b) (4), which can be present at a level of NMT [redacted] (b) (4) % in the drug product [in accordance with ICH Q3B(R2)], has been adequately qualified?

FDA Response:
No, we do not concur. [redacted] (b) (4) **However, you have not provided adequate data to support the conclusion that the level of** [redacted] (b) (4) **formed in humans is sufficient to provide adequate coverage for the total daily dose of** [redacted] (b) (4) **that could occur via use of your drug product with the proposed** [redacted] (b) (4) **% specification.**

The submitted literature references, as well as additional references identified by the Agency, describing the toxicology of [redacted] (b) (4) **are not up to current toxicology standards and therefore may not be used to support the safety of a specification** [redacted] (b) (4) **ICH Q3A/B(R2) guidelines.**

In the absence of adequate data to support your conclusion that [redacted] (b) (4) **or provide adequate qualification. In order to provide adequate qualification:**

- **You must complete a minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**

- **In addition, you must conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. In this case, a study of 90-days duration should be completed.**

— **Alternatively, you may be able to justify the safety of a drug product degradant via comparative analytical studies that demonstrate that the levels of the degradant in your drug product are equal to or below the levels found in the referenced drug product. If you elect to pursue this approach, refer to the FDA guidance for industry: ANDAs: *Impurities in Drug Products*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072861.pdf.**

Discussion:

(b) (4) The Division stated that USP specifications are not appropriate because is it not always clear that the data supporting the USP specifications have been evaluated by the Agency, rather, ICH guidelines should be followed. However, the Division will consider a comparability approach, using actual data generated from batches of the referenced product. The Division recommended assessing (b) (4) levels close to the expiry of the referenced product. (b) (4) -

(b) (4)

Question 8.

Does the Agency concur that the strategy to characterize steady-state PK is adequate for approval, if additional data are supportive?

FDA Response:

Your general approach to simulate the steady-state PK of morphine based on single-dose data appears reasonable, provided your product demonstrates bioequivalence and a similar PK profile to the listed drug. However, describe the specific details of the methodology at the time of NDA submission.

Conduct all future PK studies and clinical studies to support your NDA submission and labeling using the final to-be-marketed formulations. From all possible PK studies, provide PK parameters (C_{max}, AUC, T_{max}) for the test product along with intra-subject and inter-subject variability. If data from any subjects are not included, indicate the specific reasons for exclusion of the subjects (adverse events, etc.).

Discussion:

There was no discussion of this question.

Question 9.

Does the Agency concur with the strategy to obtain a biowaiver in support of both the 30 and 60 mg (b) (4) *dosage strengths, if the results from forthcoming studies are supportive?*

FDA Response:

Yes. We generally agree with your proposed strategy to obtain a biowaiver in support of both the 30 and 60 mg strengths. However, the final determination on granting biowaivers for the 30 and 60 mg strengths will be made during NDA review pending results of the forthcoming studies.

Discussion:

There was no discussion of this question.

Question 10.

Does the Agency concur that based on the results from the in vitro alcohol interaction data, in view of the Agency's previous guidance from the PIND meeting, dose dumping for Egalet®-001 (morphine PR) Tablets has adequately been addressed?

FDA Response:

Before we can concur, we must review the in vitro alcohol interaction data with 5, 10, 20 and 40% alcohol in 0.1N HCl and in QC dissolution medium. It is not clear what QC dissolution medium you used. (b) (4) **Clarify your QC dissolution medium.**

(b) (4) **. We also could not find the data with 10 and 20 % alcohol. Submit f2 data with all alcohol concentrations, both in 0.1N HCl and in your QC dissolution medium. In case, f2 criteria (>50) is/are not met, explain the clinical significance of the findings.**

We must review all the information described above before we can make further comment on the appropriateness of your in vitro alcohol dose dumping data.

In your report, include the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol-induced dose-dumping study.

Discussion:

There was no discussion of this question.

Additional Nonclinical Comments

In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product and how these levels compare to ICH Q3A(R2) and ICH Q3B(R2) qualification thresholds and determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.

- **NOTE: We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity or degradant that exceeds the ICH qualification thresholds.**

New excipients must be adequately qualified for safety. Studies must be submitted to the IND in accordance with the guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf. As noted in the guidance, "the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently *proposed level of exposure, duration of exposure, or route of administration.*" (emphasis added).

(b) (4)

, which is a structural alert for mutagenicity. Therefore, the specification for these impurities in the drug substance must be reduced to reflect a maximal daily intake of NMT 1.5 mcg/day or adequate safety qualification must be provided. We recommend that you consult with your DMF holder to determine the levels of these impurities in the drug substance you are obtaining and if needed, to decrease the limit of these impurities.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of the criteria apply at this time to your application, you are exempt from these requirements/ Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft

guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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