

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208603Orig1s000

OTHER REVIEW(S)

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 208603 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: ARYMO Established/Proper Name: morphine sulfate Dosage Form: Extended-Release Tablets Strengths: 15 mg, 30 mg, 60 mg Route(s) of Administration: Oral		
Applicant: Egalet, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: 12/14/2015 Date of Receipt: 12/14/2015 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: 10/14/2016		Action Goal Date (if different): 1/9/2017
Filing Date: 2/12/2016		Date of Filing Meeting: 1/20/2016
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☒ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: <i>If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		☐ 351(a) ☐ 351(k)

Review Classification: The application will be a priority review if: - A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) - The product is a Qualified Infectious Disease Product (QIDP) - A Tropical Disease Priority Review Voucher was submitted - A Pediatric Rare Disease Priority Review Voucher was submitted		☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher		
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐		
Part 3 Combination Product? ☐ If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults		☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)		
☐ Fast Track Designation ☐ Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:		☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)		
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 117317				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.	☒	☐		
Are the established/proper and applicant names correct in electronic archive? If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.	☒	☐		

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

Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	☐	☒																		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.	☐	☒																		
Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm If yes, please list below: <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td>206544</td> <td>Morphabond</td> <td>M-189</td> <td>Oct 2, 2018</td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	206544	Morphabond	M-189	Oct 2, 2018									☒	☐		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
206544	Morphabond	M-189	Oct 2, 2018																	
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>																				
If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement [see 21 CFR 314.50(i)(1)(i)(C) and 314.54]? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm If no, include template language in the 74-day letter. Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)] Note: Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.	☒	☐																		

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	☐	☒		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(14)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	☐	☐	☐	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	☐	☐	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	☐	☐	☐	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i>s/<i>NDA</i> efficacy supplements) or under 21 CFR 601.2 (<i>BLA</i>s/<i>BLA</i> efficacy supplements) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) If no, explain.	☐	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	☐	☐	☐	
Forms and Certifications				
<i>Electronic</i> forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	☒	☐		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	☒	☐		
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	☐	☐	☒	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> For non-NMEs: Date of consult sent to Controlled Substance Staff : 1/13/2016	☐	☐	☐	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	☐	☒		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☐	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☐	☐	☐	
<u>BPCA:</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³</i>	☐	☒		

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

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

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Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	☒	☐	☐	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	☒	☐	☐	
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☐ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	☒	☐		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	☐	☐	☐	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>	☒	☐	☐	

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	☒	☐		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	☒	☐	☐	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	☒	☐	☐	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	☒	☐	☐	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	☐	☒	☐	
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	☐	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s):	☐	☐		
Any Special Protocol Assessments (SPAs)? Date(s):	☐			

ATTACHMENT

MEMO OF FILING MEETING

DATE: 1/20/2016

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Christopher Hilfiger	Y
	CPMS/TL:	Parinda Jani	N
Cross-Discipline Team Leader (CDTL)	John Feeney		Y
Division Director/Deputy	Sharon Hertz/Ellen Fields		Y
Office Director/Deputy			
Clinical	Reviewer:	John Hariadi	Y
	TL:	John Feeney	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
OTC Labeling Review (for OTC products)	Reviewer:		
	TL:		
Clinical Microbiology (for antimicrobial products)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Srikanth Nallani	Y
	TL:	Yun Xu	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	N/A	
	TL:		

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Beth Bolan	Y
	TL:	Dan Mellon	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Ciby Abraham	Y
	RBPM:	Steven Kinsley	Y
• Drug Substance	Reviewer:	Debasis Ghosh	N
• Drug Product	Reviewer:	Christopher Hough	N
• Process	Reviewer:	Haitao Li	N
• Microbiology	Reviewer:	N/A	
• Facility	Reviewer:	Frank Wackes	N
• Biopharmaceutics	Reviewer:	An-Chi Lu	N
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	WALKER, MORGAN A	N
	TL:	LASHAWN M GRIFFITHS	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	LEE, KOUNG U	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	James Schlick	N
	TL:	Vicky Borders-Hemphill	N
OSE/DRISK (REMS)	Reviewer:	KIMBERLY LEHRFELD	N
	TL:	CYNTHIA L LACIVITA	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	Jim Tolliver	Y
	TL:	Michael Klein	N
Other reviewers/disciplines			
Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees			

FILING MEETING DISCUSSION:

GENERAL 505(b)(2) filing issues: - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? - Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO BA/BE Studies to MS Contin
Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO
Electronic Submission comments List comments:	☐ Not Applicable ☒ No comments

CLINICAL Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain: Site Inspected within the past 2 years	☐ YES ☒ NO
- Advisory Committee Meeting needed? Comments: All ER opioids to AC Meetings <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	☒ YES Date if known: ☐ NO ☐ To be determined Reason:
If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☐ Not Applicable ☐ YES ☒ NO
CONTROLLED SUBSTANCE STAFF Abuse Liability/Potential Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> Is the product an NME?	☐ YES ☒ NO
<u>Environmental Assessment</u> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? Comments:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> Establishment(s) ready for inspection? Comments:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u> Comments:	☐ Review issues for 74-day letter
<u>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</u> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Sharon Hertz Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAAs completed: April 2016

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
01/09/2017

PMR/PMC Development Template

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

NDA # NDA 208603
Product Name: ARYMO ER (morphine sulfate) extended-release tablets

PMR Description: 3033-1 A prospective, observational study designed to quantify the serious risks of misuse, abuse, and addiction associated with long-term use of opioid analgesics for management of chronic pain among patients prescribed ER/LA opioid analgesics.

This study (b) (4) address at a minimum the following specific (b) (4)

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

PMR Schedule Milestones:	Final Protocol Submission:	11/2015
	Interim Report (Cumulative Enrollment of 470 patients)	5/2017
	Interim Report (Cumulative Enrollment of 1,042 patients)	9/2017
	Interim Report (Cumulative Enrollment of 1,609 patients)	1/2018
	Interim Report (Cumulative Enrollment of 2,300 patients)	6/2018
	Study Completion:	10/2019
	Final Report Submission:	3/2020

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

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

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

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

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

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

- ☐ Analysis of spontaneous postmarketing adverse events?

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

- ☐ Analysis using pharmacovigilance system?

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

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

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

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

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

The initial type of study that would be anticipated would be a prospective epidemiological study to measure the incidences of the adverse outcomes listed above. However, tools to measure both the risk factors and outcomes have not been validated. As such, validation studies are required prior to the epidemiological studies (see other PMRs). It may be determined, if the outcome codes do not validate well, that other types of studies or clinical trials are needed.

Required

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

Continuation of Question 4

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

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

Agreed upon:

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

- ☐ Other

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

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA #	NDA 208603						
Product Name:	ARYMO ER (morphine sulfate) extended-release tablets						
PMR Description:	3033-2 An observational study designed to measure the incidence and predictors of opioid overdose and death (OOD), as well as opioid abuse/addiction, using patient health records, insurance claims, and death records. a. Estimate the incidence of abuse/addiction, overdose, and death associated with long-term use of opioid analgesics for chronic pain. Stratify overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of abuse/addiction, overdose, and death. b. Evaluate and quantify other risk factors for abuse/addiction, overdose, and death associated with long-term use of opioid analgesics for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify overdose by intentionality wherever possible.						
PMR Schedule Milestones:	<table><tr><td>Final Protocol Submission:</td><td>11/2014</td></tr><tr><td>Study Completion:</td><td>4/2019</td></tr><tr><td>Final Report Submission:</td><td>9/2019</td></tr></table>	Final Protocol Submission:	11/2014	Study Completion:	4/2019	Final Report Submission:	9/2019
Final Protocol Submission:	11/2014						
Study Completion:	4/2019						
Final Report Submission:	9/2019						

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

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

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

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

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

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

- ☐ Analysis of spontaneous postmarketing adverse events?

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

- ☐ Analysis using pharmacovigilance system?

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

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

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

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

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

The initial type of study that would be anticipated would be an epidemiological study in large databases to measure the incidences of the adverse outcomes listed above. However, neither the codes for many of the risk factors nor those for these outcomes have been validated. As such, validation studies are required prior to the epidemiological studies (see other PMRs). It may be determined, if the outcome codes do not validate well, that other types of studies or clinical trials are needed.

Required

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

Continuation of Question 4

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

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

Agreed upon:

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

- ☐ Other

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

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- ☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA #	NDA 208603		
Product Name:	ARYMO ER (morphine sulfate) extended-release tablets		
PMR Description:	3033-3 A prospective observational study designed to assess the content validity and patient interpretation of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ). Patient understanding of the concepts of misuse and abuse will also be obtained.		
PMR Schedule Milestones:	Final Protocol Submission:	04/2015	
	Study Completion:	10/2015	
	Final Report Submission:	01/2016	

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

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

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

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

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death.

The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, the outcomes need to be validated, including measures of opioid-related adverse events.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

An observational study would likely be conducted that includes identifying patients who have been prescribed opioids for long-term use, administering a specifically designed survey to identify patients that misuse and/or abuse opioids, and conducting an interview, chart review, or a similar activity to determine if the patients understand the survey instrument, and if the instrument measures what is designed to assess.

Required

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

☐ Dosing trials

Continuation of Question 4

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

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

☐ Immunogenicity as a marker of safety

☐ Other (provide explanation)

Agreed upon:

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

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

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

☐ Dose-response study or clinical trial performed for effectiveness

☐ Nonclinical study, not safety-related (specify)

☐ Other

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

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

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

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

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

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

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

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

☐ There is not enough existing information to assess these risks

☐ Information cannot be gained through a different kind of investigation

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA #	NDA 208603		
Product Name:	ARYMO ER (morphine sulfate) extended-release tablets		
PMR Description:	3033-4 An observational study to evaluate the validity and reproducibility of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ), which will be used to identify opioid abuse and misuse behaviors among participants who have chronic pain which requires long-term opioid analgesic use.		
PMR Schedule Milestones:	Final Protocol Submission:	04/2015	
	Study Completion:	10/2016	
	Final Report Submission:	02/2017	

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

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

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

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

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death.

The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, the outcomes need to be validated, including measures of opioid-related adverse events.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

An observational study would likely be conducted that includes identifying patients who fulfill the criteria of long-term opioid use, administering a specifically designed survey instrument to identify opioid abuse and misuse behaviors, and then conducting a chart review or a similar activity to determine whether the identified patients actually meet the case definition.

Required

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

Continuation of Question 4

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

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

☐ Immunogenicity as a marker of safety

☐ Other (provide explanation)

Agreed upon:

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

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

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

☐ Dose-response study or clinical trial performed for effectiveness

☐ Nonclinical study, not safety-related (specify)

☐ Other

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

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

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

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

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

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

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

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

☐ There is not enough existing information to assess these risks

☐ Information cannot be gained through a different kind of investigation

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA #	NDA 208603		
Product Name:	ARYMO ER (morphine sulfate) extended-release tablets		
PMR Description:	3033-5 An observational study to validate measures of prescription opioid Substance Use Disorder and addiction in patients who have received or are receiving opioids for chronic pain..		
PMR Schedule Milestones:	Final Protocol Submission:	04/2015	
	Study Completion:	12/2016	
	Final Report Submission:	05/2017	

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

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

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

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

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death.

The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, the outcomes need to be validated, including measures of opioid-related adverse events.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

An observational study would likely be conducted that includes identifying patients who have been prescribed opioids for long-term use, administering a specifically designed survey instrument (PRISM-5-Op) to identify those with prescription opioid Substance Use Disorder and addiction, and then conducting a chart review or a similar activity to determine whether the identified patients actually meet the case definition.

Required

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

☐ Dosing trials

Continuation of Question 4

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

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

☐ Immunogenicity as a marker of safety

☐ Other (provide explanation)

Agreed upon:

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

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

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

☐ Dose-response study or clinical trial performed for effectiveness

☐ Nonclinical study, not safety-related (specify)

☐ Other

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

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

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

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

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

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

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

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

☐ There is not enough existing information to assess these risks

☐ Information cannot be gained through a different kind of investigation

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA #	NDA 208603		
Product Name:	ARYMO ER (morphine sulfate) extended-release tablets		
PMR Description:	3033-6 An observational study to develop and validate an algorithm using coded medical terminologies and other electronic healthcare data to identify opioid-related overdose and death.		
PMR Schedule Milestones:	Final Protocol Submission:	11/2014	
	Study Completion:	09/2016	
	Final Report Submission:	12/2016	

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

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

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

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

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death.

The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, algorithms must be developed to reliably identify opioid-related adverse events of misuse, abuse, addiction, overdose and death solely using coded medical terminologies (e.g., ICD9, ICD10, SNOMED).

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

An observational study would likely be conducted that includes developing a process or algorithm to reliably identify patients using coded medical terminologies (e.g., ICD9, ICD10, SNOMED) for the opioid-related adverse events of overdose and death, and validating that process or algorithm with chart review or a similar activity.

Required

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

Continuation of Question 4

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

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

☐ Immunogenicity as a marker of safety

☐ Other (provide explanation)

Agreed upon:

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

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

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

☐ Dose-response study or clinical trial performed for effectiveness

☐ Nonclinical study, not safety-related (specify)

☐ Other

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

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

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

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

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

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

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

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

☐ There is not enough existing information to assess these risks

☐ Information cannot be gained through a different kind of investigation

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA #	NDA 208603		
Product Name:	ARYMO ER (morphine sulfate) extended-release tablets		
PMR Description:	3033-7 An observational study to develop and validate an algorithm using coded medical terminologies to identify patients experiencing prescription opioid abuse or addiction, among patients receiving an ER/LA opioid analgesic.		
PMR Schedule Milestones:	Final Protocol Submission:	11/2014	
	Study Completion:	10/2016	
	Final Report Submission:	01/2017	

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

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

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

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

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death.

The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, the coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify opioid-related adverse events of misuse, abuse, addiction, overdose, and death need to be validated.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

An observational study would likely be conducted that includes identifying patients with a specifically developed algorithm solely using coded medical terminologies (e.g., ICD9, ICD10, SNOMED) for opioid-related adverse events: misuse abuse, and addiction, and then conducting chart review or a similar activity to determine whether the identified patients actually meet the clinical definition. The validation process would be conducted in multiple data resources to ensure applicability in diverse populations and settings.

Required

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

☐ Drug interaction or bioavailability studies or clinical trials

☐ Dosing trials

Continuation of Question 4

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

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

☐ Immunogenicity as a marker of safety

☐ Other (provide explanation)

Agreed upon:

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

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

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

☐ Dose-response study or clinical trial performed for effectiveness

☐ Nonclinical study, not safety-related (specify)

☐ Other

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

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

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

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

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

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

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

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

☐ There is not enough existing information to assess these risks

☐ Information cannot be gained through a different kind of investigation

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA #	NDA 208603	
Product Name:	ARYMO ER (morphine sulfate) extended-release tablets	
PMR Description:	3033-8 An observational study using coded medical terminologies and other electronic healthcare data to define and validate doctor and/or pharmacy shopping outcomes by examining their association with abuse and/or addiction.	
PMR Schedule Milestones:	Final Protocol Submission:	03/2015
	Study Completion:	10/2017
	Final Report Submission:	01/2018

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

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

The data needed to validate “doctor/pharmacy shopping” as outcomes suggestive of misuse, abuse, and/or addiction would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

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

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death.

The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, the outcome of doctor/pharmacy shopping needs to be defined and validated, and its relationship to misuse, abuse, and/or addiction must be better characterized.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

An observational study would likely be conducted that includes identifying patients who were prescribed opioids and conducting chart reviews or similar activities to determine if there is a pattern of activity suggestive of doctor and/or pharmacy shopping and identify common characteristics of those patients.

Required

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

Continuation of Question 4

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

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

☐ Immunogenicity as a marker of safety

☐ Other (provide explanation)

Agreed upon:

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

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

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

☐ Dose-response study or clinical trial performed for effectiveness

☐ Nonclinical study, not safety-related (specify)

☐ Other

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

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

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

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

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

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

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

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

☐ There is not enough existing information to assess these risks

☐ Information cannot be gained through a different kind of investigation

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA #	NDA 208603		
Product Name:	ARYMO ER (morphine sulfate) extended-release tablets		
PMR Description:	3033-9 An observational study using a validated patient survey to evaluate the association between doctor/pharmacy shopping outcomes and self-reported misuse and abuse.		
PMR Schedule Milestones:	Final Protocol Submission:	03/2015	
	Study Completion:	09/2018	
	Final Report Submission:	12/2018	

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

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

The data needed to validate “doctor/pharmacy shopping” as outcomes suggestive of misuse, abuse, and/or addiction would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

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

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use , including misuse, abuse, addiction, overdose and death.

The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, the outcome of doctor/pharmacy shopping needs to be defined and validated, and its relationship to misuse, abuse, and/or addiction must be better characterized.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

An observational study would likely be conducted that includes identifying patients who meet one or more definitions of doctor and/or pharmacy shopping, and then conducting chart review or a similar activity to determine whether the identified patients have an indication of opioid misuse and/or abuse.

Required

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

Continuation of Question 4

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

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

☐ Immunogenicity as a marker of safety

☐ Other (provide explanation)

Agreed upon:

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

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

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

☐ Dose-response study or clinical trial performed for effectiveness

☐ Nonclinical study, not safety-related (specify)

☐ Other

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

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

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

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

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

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

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

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

☐ There is not enough existing information to assess these risks

☐ Information cannot be gained through a different kind of investigation

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA #	NDA 208603		
Product Name:	ARYMO ER (morphine sulfate) extended-release tablets		
PMR Description:	3033-10 An observational study using medical record review to evaluate the association between doctor/pharmacy shopping outcomes and patient behaviors suggestive of misuse, abuse and/or addiction.		
PMR Schedule Milestones:	Final Protocol Submission:	03/2015	
	Study Completion:	03/2017	
	Final Report Submission:	06/2017	

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

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

The data needed to validate “doctor/pharmacy shopping” as outcomes suggestive of misuse, abuse, and/or addiction would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

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

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death.

The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, the relationship between doctor/pharmacy shopping and misuse, abuse, and/or addiction needs to be more clearly elucidated.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

An observational study would likely be conducted that includes identifying patients who meet one or more definitions of “doctor/pharmacy shopping”, and then conducting chart review or a similar activity to determine whether the patterns and characteristics of behaviors indicative of misuse, abuse, or addiction can also be identified in the patient population.

Required

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

Continuation of Question 4

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

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

☐ Immunogenicity as a marker of safety

☐ Other (provide explanation)

Agreed upon:

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

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

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

☐ Dose-response study or clinical trial performed for effectiveness

☐ Nonclinical study, not safety-related (specify)

☐ Other

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

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

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

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

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

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

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

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

☐ There is not enough existing information to assess these risks

☐ Information cannot be gained through a different kind of investigation

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA #	NDA 208603		
Product Name:	ARYMO ER (morphine sulfate) extended-release tablets		
PMR Description:	3033-11	Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following the long-term use of high-dose ER/LA opioid analgesics for at least one year to treat chronic pain. Include an assessment of risk relative to efficacy.	
PMR Schedule Milestones:	Final Protocol Submission:	11/2014	
	Trial Completion:	02/2019	
	Final Report Submission:	08/2019	

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

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

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

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

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

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

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

Required

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

Continuation of Question 4

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

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

☐ Immunogenicity as a marker of safety

☐ Other (provide explanation)

Agreed upon:

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

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

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

☐ Dose-response study or clinical trial performed for effectiveness

☐ Nonclinical study, not safety-related (specify)

☐ Other

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

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

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

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

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

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

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

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

☒ There is not enough existing information to assess these risks

☒ Information cannot be gained through a different kind of investigation

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA/BLA # NDA 208603

Product Name: ARYMO ER (morphine sulfate) extended-release tablets

PMR Description: 3148-1 In order to provide the baseline data to support the hypothesis-testing studies required under PMR 3148-2, conduct a descriptive study that analyzes data on the following:

(1) utilization of ARYMO ER (morphine sulfate) extended-release tablets and selected comparators. Reports should include nationally-projected quarterly retail dispensing, overall and by age group and census region;

AND

(2) abuse of ARYMO ER (morphine sulfate) extended-release tablets and related clinical outcomes. These studies should utilize multiple data sources in different populations to establish the scope and patterns of abuse for ARYMO ER (morphine sulfate) extended-release tablets as well as mutually agreed-upon, selected comparators to provide context.

- Data should include route-specific abuse outcomes, be nationally-representative or from multiple large geographic areas, and use meaningful measures of abuse.
- Additional information, either qualitative or quantitative, from sources such as internet forums, spontaneous adverse event reporting, or small cohort studies may also be included to help better understand abuse of this drug, including routes and patterns of abuse in various populations.
- Formal hypothesis testing is not necessary during this phase, but provide information on the precision of abuse-related outcome estimates (e.g. 95% confidence intervals for quarterly estimates) and calculate utilization-adjusted outcome estimates where possible.

PMR Schedule Milestones:

Draft Protocol Submission:

05/2017

Final Protocol Submission:

09/2017

Study Completion:

09/2018

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

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

This PMR requires marketing and use in the community over the long-term in order to assess whether the abuse-deterrent characteristics of ARYMO ER actually deter abuse of the product in “real world” use.

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

FDA has determined that the sponsor must conduct individual post-marketing studies of ARYMO ER to assess the known serious risks of misuse, abuse, and their consequences, and in particular to assess whether the opioid antagonist properties of ARYMO ER that are intended to deter misuse and abuse actually result in a decrease in misuse and abuse and their consequences.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

- ☐ Analysis of spontaneous postmarketing adverse events?

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

☐ Analysis using pharmacovigilance system?

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

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

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

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

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

Descriptive observational studies to document the patterns of use of ARYMO ER and describe the patterns of misuse and abuse that are occurring in the "real world".

Required

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

Continuation of Question 4

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

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

☐ Immunogenicity as a marker of safety

☐ Other (provide explanation)

Agreed upon:

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

☐ Other

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

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA/BLA # NDA 208603
Product Name: ARYMO ER (morphine sulfate) extended-release tablets

PMR Description: 3148-2: Conduct formal observational studies to assess whether the properties intended to deter misuse and abuse of ARYMO ER (morphine sulfate) extended-release tablets actually result in a meaningful decrease in misuse and abuse, and their consequences, addiction, overdose, and death, in post-approval settings. The studies should allow FDA to assess the impact, if any, attributable to the abuse-deterrent properties of ARYMO ER (morphine sulfate) extended-release tablets and should incorporate recommendations contained in *Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry* (April 2015). Assessing the impact of the abuse-deterrent formulation on the incidence of clinical outcomes, including overdose and death, is critical to fulfilling this PMR. Any studies using electronic healthcare data should use validated outcomes and adhere to guidelines outlined in FDA's *Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoeconomic Safety Studies Using Electronic Healthcare Data*.

PMR Schedule Milestones:	Draft Protocol	05/2019
	Final Protocol Submission:	09/2019
	Study Completion:	09/2021
	Final Report Submission:	03/2022
	Other: N/A	N/A

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

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

This PMR requires marketing and use in the community over the long-term in order to assess whether the abuse-deterrent characteristics of ARYMO ER actually deter abuse of the product in "real world" use.

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

FDA has determined that the sponsor must conduct individual post-marketing studies of ARYMO ER to assess the known serious risks of misuse, abuse, and their consequences, and in particular to assess whether the properties of ARYMO ER that are intended to deter misuse and abuse actually result in a decrease in misuse and abuse and their consequences.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

- ☐ Analysis of spontaneous postmarketing adverse events?

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

- ☐ Analysis using pharmacovigilance system?

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

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

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

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

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

The design of the hypothesis-testing studies for ARYMO ER will be informed by the patterns of use and the patterns of misuse/ abuse documented in PMR XXXX-2. The hypothesis testing studies must incorporate recommendations contained in the FDA draft guidance Abuse-Deterrent Opioids—Evaluation and Labeling (January 2013) and must allow FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of ARYMO ER. In particular, post-marketing studies for ARYMO ER must include individual assessments of all relevant routes of abuse and must employ multiple appropriate comparators, including but not limited to 1) immediate and extended release formulations of morphine sulfate and other opioid analgesics and 2) both products with and without properties intended to deter abuse. The study program must include geographically diverse populations that include both opioid-dependent and non-dependent individuals and must address all the abuse-related outcomes of interest: misuse, abuse, addiction, overdose, and death.

Required

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

Continuation of Question 4

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

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

Agreed upon:

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

- ☐ Other

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

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?

- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- ☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

NDA/BLA # NDA 208603
 Product Name: ARYMO ER (morphine sulfate) extended-release tablets
 PMR/PMC Description: 3148-3 Analyze the PEO product employed in Arymo ER for low molecular weight impurities. Identify and quantitate the impurities. Submit a toxicological risk assessment for the exposure to the impurities taking into consideration the maximum theoretical daily dose of Arymo ER.

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

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

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

The excipient is in FDA-approved drug products, (b) (4). Given the long history of use of this class of excipients and the likelihood that most individuals will not reach the maximum theoretical daily dose, more definitive characterization of these impurities was considered acceptable to be completed post marketing.

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

(b) (4) review of the existing distribution data suggest that (b) (4) % of the material is absorbed systemically. At the maximum daily dose, this would result in absorption of (b) (4) mg of material. These are likely lower molecular weight impurities that could include (b) (4). Once identified, a toxicological risk assessment should be completed. The goal of the PMR is to identify the impurities and determine if specifications should be put in place to control them consistent with modern manufacturing quality control methods.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

The study is a chemical analysis of the excipient. Once the impurities are identified, a toxicological risk assessment should be completed.

Required

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

Continuation of Question 4

- ☒ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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

Agreed upon:

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

-
- ☐ Other
-

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

NDA 208603

ARYMO ER (morphine sulfate) extended-release tablets

PMR/PMC Description: 3148-4 Conduct an embryo-fetal development study in the rat model to assess the potential impact of (b) (4) on development. The study must be designed to adequately qualify the safety of the low molecular weight PEO components (impurities/degradants) in (b) (4) when the product is consumed up to the MTDD of Arymo ER.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	05/2018
	Study/Trial Completion:	11/2018
	Final Report Submission:	05/2019
	Other: N/A	N/A

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

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

The excipient is in FDA-approved drug products. (b) (4)
Given the long history of use of this class of excipients and the likelihood that most individuals will not reach the maximum theoretical daily dose, more definitive characterization of these impurities was considered acceptable to be completed post marketing.

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

3. I Embryo-fetal developmental toxicology studies in two species (rat and rabbit models) are generally required to adequately inform the safety of any excipient. Although these studies were not required in the past based on standards at the time, (b) (4). Embryo-fetal development studies are therefore warranted for this drug product. If adverse effects are noted, the labeling would be updated to reflect the added risk.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

The study is an in vivo embryo-fetal developmental toxicology study using the rat model.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial

☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

NDA 208603

ARYMO ER (morphine sulfate) extended-release tablets

PMR/PMC Description: 3148-5 Conduct an embryo-fetal development study in the rabbit model to assess the potential impact of (b) (4) on development. The study must be designed to adequately qualify the safety of the low molecular weight PEO components (impurities/degradants) in (b) (4) when the product is consumed up to the MTDD of Arymo ER.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	06/2018
	Study/Trial Completion:	03/2019
	Final Report Submission:	09/2019
	Other:	N/A

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

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

The excipient is in FDA-approved drug products, (b) (4). Given the long history of use of this class of excipients and the likelihood that most individuals will not reach the maximum theoretical daily dose, more definitive characterization of these impurities was considered acceptable to be completed post marketing.

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

Embryo-fetal developmental toxicology studies in two species (rat and rabbit models) are generally required to adequately inform the safety of any excipient. Although these studies were not required in the past based on standards at the time (b) (4). Embryo-fetal development studies are therefore warranted for this drug product. If adverse effects are noted, the labeling would be updated to reflect the added risk.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

The study is an in vivo embryo-fetal developmental toxicology study using the rabbit model.

Required

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

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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

Agreed upon:

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

-
- ☐ Other
-

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

NDA 208603

ARYMO ER (morphine sulfate) extended-release tablets

PMR/PMC Description: 3148-6 Conduct a pre- and post-natal development study in the rat model to assess the potential impact of (b) (4) on development. The study must be designed to adequately qualify the safety of the low molecular weight PEO components (impurities/degradants) in (b) (4) when the product is consumed up to the MTDD of Arymo ER.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	01/2019
	Study/Trial Completion:	11/2019
	Final Report Submission:	05/2020
	Other:	N/A

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

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

The excipient is in FDA-approved drug products, (b) (4). Given the long history of use of this class of excipients and the likelihood that most individuals will not reach the maximum theoretical daily dose, more definitive characterization of these impurities was considered acceptable to be completed post marketing.

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

A pre- and post-natal developmental toxicology study is generally required to adequately inform the safety of any excipient. Although these studies were not required in the past based on standards at the time, (b) (4). A pre- and post-natal development study is therefore warranted for this drug product. If adverse effects are noted, the labeling would be updated to reflect the added risk.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

The study is an in vivo pre-and post-natal developmental toxicology study using the rat model.

Required

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

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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

Agreed upon:

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

-
- ☐ Other
-

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

NDA/BLA # NDA 208603
Product Name: ARYMO ER (morphine sulfate) extended-release tablets

PMC Description: 3148-7 There is some preliminary evidence of possible degradation of polyethylene oxide (PEO) over time, which could potentially alter the abuse-deterrent properties of the drug product. To ensure the continued performance of in-vitro abuse-deterrent formulation (ADF) properties of the marketed ARYMO ER through shelf-life and during the life-cycle of the product, perform the following Category 1 testing as part of the stability protocol, on one commercial scale batch at 0, 6-months, 12-months and annually thereafter to the end of shelf-life. Perform the testing on intact tablets, manipulated tablets (using the optimal method for smallest particle size), and pre-treated tablets (e.g., heating in an oven or microwaving).

Physical Manipulations and particle size measurement:

1. Single-step manipulation using the pre-defined optimal manipulation conditions for ARYMO ER, identified in the pre-approval category 1 studies
2. Measurement of the particle size distribution using the standardized method

Injectability/Syringeability Study:

1. Small volume extractions using 10 mL of tap water, saline and 50% ethanol.
2. Determine the amount of morphine recovered and the viscosity of the samples.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	06/2017
Study Completion:	12/2020
Interim Annual Report	09/2018
Interim Annual Report	03/2019
Interim Annual Report	03/2020
Final Report Submission:	03/2021

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

☐ Unmet need

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

The Category One Abuse Deterrent Studies were conducted during pharmaceutical development with the supporting data submitted to the NDA. There is preliminary evidence of possible degradation of PEO over time during the shelf life of the product. Breakdown of PEO could alter the ADF properties of the drug product. Therefore repeated Category 1 testing as part of the stability program, would support continued ADF labeling of the product.

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

3. I

The ADF labeling for this product is partly supported by the pre-approval Category 1 data. Key attributes of the product have been identified (hardness, extractability and injectability) as the premise for granting the category 1 claim. Therefore the ongoing stability study, to test the hardness, extractability and injectability, would ensure the continued abuse deterrent properties of the drug product throughout shelf life

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

- ☐ Analysis of spontaneous postmarketing adverse events?

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

- ☐ Analysis using pharmacovigilance system?

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

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

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

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

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

The study is the determination of injectability and extractability of the drug product, under long term storage conditions, to ensure the continued abuse deterrent properties of the drug product.

Required

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

Continuation of Question 4

Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

- ☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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

Agreed upon:

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

☐ Nonclinical study, not safety-related (specify)

☒ Other

Chemical Manipulation and Extraction studies conducted during the stability studies.

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

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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
01/06/2017

JUDITH A RACOOSIN
01/06/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

Division of Pediatric and Maternal Health Memorandum

Date: September 23, 2016 **Date Consulted:** February 2, 2016

From: Miriam Dinatale, D.O., Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Through: Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Division of Anesthesia, Analgesia and Addiction Products

Drug: Arymo ER (morphine sulfate) extended-release tablets

NDA: 208603

Applicant: Egalet US Inc.

Subject: Pregnancy and Lactation labeling

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

Materials Reviewed:

- DPMH consult request dated February 2, 2016, DARRTS Reference ID 3881393
- Applicant's submitted background package for NDA 208603, Arymo ER

Consult Question:
DAAAP is requesting that DPMH assist in the reviewing labeling for the new PLLR format.

INTRODUCTION

The Division of Anesthesia, Analgesia and Addiction Products (DAAAP) consulted the Division of Pediatric and Maternal Health (DPMH) on February 2, 2016, to provide input for appropriate labeling of the pregnancy and lactation subsections of Arymo ER (morphine sulfate) labeling.

REGULATORY HISTORY

On December 14, 2015, Egalet US Inc., submitted a 505 (b)(2) New Drug Application (NDA) for Arymo ER (morphine sulfate) extended-release tablets (NDA 208603) for the proposed indication of analgesia for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate. The Referenced Listed Drugs (RLD) is MS Contin (morphine sulfate), NDA 019516. The active ingredient, morphine sulfate, in Arymo ER is the same as the RLD, but the drug product contains abuse-deterrent properties based on Egalet's proprietary Guardian Technology platform.¹

BACKGROUND

Opioids and Pregnancy

Opioid medications may be needed during pregnancy to manage severe pain associated with many conditions, including both acute and chronic medical conditions and surgical procedures.² The prevalence of opioid abuse or dependence during pregnancy increased from 0.17% (1998) to 0.39% (2011).³ Recent studies indicate that 14 to 22% of pregnant women in the US receive an opioid prescription during their pregnancy.⁴

Morphine and Drug Characteristics⁵

Morphine is an opioid agonist with affinity for mu receptors in the brain, spinal cord and peripheral organs. Morphine is metabolized via glucuronidation to produce two major metabolites [morphine-3-glucuronide (M3G)-50% and morphine-6-glucuronide (M6G)- 5-15%] and via sulfation in the liver to produce morphine-3-etheral sulfate). Morphine has a molecular weight of 285.34 Daltons, a half-life of 2 to 4 hours after intravenous administration (with a reported terminal half-life of up to 15 hours), protein binding of 30-35% and oral bioavailability of 20-40%. Serious adverse events that can occur with use of morphine include addiction and abuse, adrenal insufficiency, respiratory depression, hypotension, sedation, coma and death.

Opioid Analgesic Drug Products' Class Labeling

On September 10, 2013, the FDA implemented safety labeling changes related to neonatal opioid withdrawal syndrome (NOWS) for extended-release/long-acting (ER/LA) opioid analgesics. The Office of Regulatory Policy received a citizen petition from the National

¹ Egalet's proprietary Guardian Technology platform: is a polymer matrix tablet technology that utilizes a novel manufacturing process, plastic injection molding, which results in tablets that are difficult to manipulate. Cover Letter from Egalet US Inc. December 14, 2015.

² Sahin, Leyla. PMHS-MHT Review- Xartemis XR (NDA 204031). 10/28/2013

³ Maeda, Ayumi. Opioid Abuse and Dependence during Pregnancy: Temporal Trends and Obstetrical Outcomes. 2014. Anesthesiology. 121(6): 1158-65.

⁴ Volkow, Nora. Opioids in Pregnancy. BMJ. 2016: 352.

(b) (4)

Advocates for Pregnant Women on October 17, 2013. On April 11, 2014, DPMH completed a review in response to the citizen's petition and discussed recommended labeling for NOWS.⁶ Newly required class labeling for opioid analgesic drug products (applies to Schedule II controlled substances with extended release or long acting (ER/LA) formulations) has been issued. As part of the class labeling, boxed warnings are required for addiction, abuse and misuse, respiratory depression (that can lead to overdose and death) and NOWS (which may be life threatening in neonates whose mothers required prolonged opioid therapy while pregnant). In addition to the boxed warnings, there is class labeling in several sections and sub-sections.⁷

Pregnancy and Lactation Labeling

On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"⁸ also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule⁹ format to include information about the risks and benefits of using these products during pregnancy and lactation.

PREGNANCY

Nonclinical Experience

Since the applicant is not the innovator for morphine sulfate, the applicant relied on animal data that appeared in MS Contin. Several reports from literature note that subcutaneous administration of morphine to mice and hamsters during organogenesis resulted in neurological, soft tissue and skeletal abnormalities at maternally toxic doses.

In one study, subcutaneous administration of morphine sulfate to pregnant mice at doses greater than or equal to 0.15 mg/kg resulted in exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternbrae, and malformed xiphoid; these effects occurred in the absence of maternal toxicity. In the hamster, morphine sulfate given subcutaneously on gestation day 8 produced exencephaly and cranioschisis. In rats treated with subcutaneous infusions of morphine during the period of organogenesis, no teratogenicity was observed. No maternal toxicity was observed in this study, however, increased mortality and growth retardation were seen in the offspring. In two studies performed in the rabbit, no evidence of teratogenicity was reported at subcutaneous doses up to 100 mg/kg.

⁶ Leyla Sahin, MD, Amy Taylor, MD, MHS. Citizen Petition and Petition for Stay regarding Neonatal Opioid Withdrawal Syndrome (NOWS) labeling changes. April 11, 2014. DARRTS Reference ID: 3488324

⁷ Draft Guidances for Industry: Analgesic Indications: Developing Drug and Biological Products (February 2014); and, Abuse Deterrent Opioids-Evaluation and Labeling (January 2013).

⁸ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

⁹ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

Published literature has reported that exposure to morphine during organogenesis in rats, hamsters, guinea pigs and rabbits resulted in the following treatment-related embryotoxicity and neonatal toxicity in one or more studies: decreased litter size, embryo-fetal viability, fetal and neonatal body weights, absolute brain and cerebellar weights, delayed motor and sexual maturation, and increased neonatal mortality, cyanosis and hypothermia.

The reader is referred to the Nonclinical Review by Beth Bolan, Ph.D. for further details.

Current Labeling for Reference Listed Drug¹⁰

Current labeling for MS Contin, which was last revised in April of 2014, includes a boxed warning and a Warnings and Precautions section describing prolonged use of MS Contin and the risk for NOWS. MS Contin labeling notes that there are no adequate and well controlled studies of morphine in pregnant women and that MS Contin should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. There is information about human data with morphine use during the first trimester of pregnancy (n=70 women) and use of morphine at any time during pregnancy (n=448 women)¹¹ and “the frequency of congenital anomalies has been reported to be no greater than expected.”

Clinical Trial Findings with Arymo ER

The applicant did not conduct studies with Arymo ER in pregnant women, and there were no reported cases of pregnancy that occurred during clinical trials with Arymo ER.

Applicant Review of Published Literature

Egalet US Inc. performed a literature search in Embase and Medline from 1987 to March 31, 2016 using the search terms “morphine and pregnancy” and reviewed several published articles including the following:

- A review article reported on 448 morphine exposures occurring at various stages of pregnancy with no evidence of increased teratogenic effects.¹²
- A review article noted that there is no significant evidence from published literature that maternal opioid use results in congenital malformations.¹³
- A prospective cohort study noted that neonatal outcomes (gestational age, prematurity, Apgar scores at 1 and 5 minutes, head circumference, arterial pH, venous pH, and stillbirths) were similar between morphine-exposed and morphine unexposed pregnancies¹⁴
- A randomized trial evaluated the effects of morphine on oxytocin concentration in the maternal plasma in women during labor.¹⁵

¹⁰ MS Contin (morphine sulfate) labeling. Drugs@FDA. Accessed 9/12/2016.

¹¹ Heinonen OP, Slone D, Shapiro S. Birth defects and drugs in pregnancy. Littleton, MA: Publishing Sciences Group; 1977

¹² Babb, et al. Treating pain during pregnancy. Can Fam Physician. 2010. 56(1); 25-27.

¹³ Bandstra, et al. Prenatal drug exposure: infant and toddler outcomes. J Addict Dis. 2010; 29(2): 245-58.

¹⁴ Dooley, et al. Narcotic tapering in pregnancy using long-acting morphine: an 18-month prospective cohort study in northwestern Ontario. Can Fam Physician. 2015. 61(2): e88-95.

¹⁵ Lindow, et al. The effect of morphine and naloxone administration on plasma oxytocin concentrations in the first state of labour. Clin Endocrinol. 1992; 37(4): 349-53.

The applicant's review of published literature is adequate. The reader is referred to the applicant's "Summary of Clinical Safety Addendum-Pregnancy and Lactation Labeling Rule" document for further details of the studies reviewed.¹⁶

DPMH's Review of Published Literature

DPMH conducted a literature search in PubMed and TERIS (Micromedex)¹⁷ using the search terms "morphine and pregnancy and fetal malformations," "morphine and pregnancy and stillbirth," "morphine and pregnancy and miscarriage/spontaneous abortion."

In addition to what the applicant included in their review of literature, DPMH reviewed one additional source that discussed morphine use during pregnancy:

Micromedex notes the following:

"Morphine does cross the placenta. Use during pregnancy only if the potential maternal benefit outweighs the potential fetal risk. Use is not recommended immediately during or immediately before labor... opioid analgesics may prolong labor by reducing the strength, duration and frequency of uterine contractions."

Previous reviews by DPMH have reviewed the effects of opioids during pregnancy. Overall, there were three case-control studies that demonstrated statistically significant associations between opioid exposure in the first trimester of pregnancy and congenital malformations^{18,19,20} and two studies that did not show an increase in congenital malformations.^{21,22} These studies were reviewed by DPMH in 2013, and the reader is referred to the DPMH Review by Leyla Sahin, MD for further details.²³

In an FDA Drug Safety Communication issued on January 9, 2015, the Agency reviewed published studies that reported on the potential risks of three types of pain medicine, including prescription non-steroidal anti-inflammatory drugs, acetaminophen and opioids, used during pregnancy. The Agency reviewed data related to opioid use (oxycodone, hydrocodone, hydromorphone, morphine and codeine) during pregnancy and evaluated the risk of birth defects of the brain, spine or spinal cord in infants born to women who took these products during the first trimester of pregnancy. The Agency found that all of the

¹⁶ EDR 2.7.4. Egalet US Inc. Clinical Safety Addendum-Pregnancy and Lactation Labeling Rule

¹⁷ TERIS is the TERatology Information Service located at University of Washington. It is an online database designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women. Accessed 9/9/16.

¹⁸ Broussard C, Rasmussen S, Reefhuis J et al Maternal treatment with opioid analgesics and risk for birth defects. American Journal of Obstetrics Gynecology. 2011; 204: 314.

¹⁹ Yazdy MM, Mitchell AA, Tinker SC, Parker SE, Werler MM. Periconceptional Use of Opioids and the Risk of Neural Tube Defects. Obstetrics and Gynecology. 2013 (122):4:838-844.

²⁰ Briggs, et al. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk, 7th ed. Philadelphia, PA: Lippincott Williams and Wilkins: 2005: 378.

²¹ Schick B, Hom M, Tolosa J, Librizzi R, Donnenfeld A. A preliminary analysis of first trimester exposure to oxycodone and hydrocodone. Reprod Toxicol. 1996;10:162.

²² Heinonen OP, Slone D, Shapiro S. Analgesics and antipyretic drugs. Birth defects and drugs in pregnancy. Littleton (MA): Publishing Sciences Group Inc; 1977. p. 286-95.

²³ DPMH review for Xartemis (oxycodone hydrochloride and acetaminophen), NDA 204031, Leyla Sahin, MD, October 30, 2013.

studies reviewed have limitations in their designs; therefore, it is not possible to draw any conclusions regarding the risks of malformations following exposure to opioids during pregnancy.²⁴

Neonatal Opioid Withdrawal Syndrome

Overall, infants of mothers who took opioids during pregnancy are at risk for NOWS, which may be life-threatening if the infant is not recognized early and does not get appropriate treatment. Infants of mothers who are using opioids throughout pregnancy should be carefully monitored for signs of withdrawal (hypertonicity, hyperactivity, twitching, seizures, high-pitched cry, tremors, vomiting, diarrhea, sneezing and tachypnea) after birth. The reader is referred to the FDA Draft Guidance for Industry related to NOWS for ER/LA opioid analgesics²⁵ and the DPMH review by Leyla Sahin, MD and Amy Taylor, MD, MHS that discusses the response to the Citizen Petition regarding NOWS labeling change for further details.²⁶

Summary

Animal reproduction studies in published literature have demonstrated an increased risk of embryofetal toxicity with the use of morphine sulfate during pregnancy. In addition, the cumulative data on opioid exposure during pregnancy and congenital malformations are very limited. The Agency found that all of the studies reviewed have limitations in their designs; therefore, it is not possible to draw any conclusions regarding the risks of malformations following exposure to opioids during pregnancy.²⁷ Given the concern for embryofetal toxicity seen in animal studies, section 8.1, Risk Summary will state the following:

Based on animal data, advise pregnant women of the potential risk to a fetus.

Arymo ER labeling will be structured in the PLLR format using ER/LA opioid labeling.

LACTATION

Current Labeling for Reference Listed Drug²⁸

Current MS Contin labeling notes that morphine has been detected in breast milk and that the morphine milk/plasma ratio (based on area under the curve) is 2.5:1. Since withdrawal symptoms can occur in breastfeeding infants when maternal administration of opioid analgesics stopped and because of the potential for adverse reactions in nursing infants, MS Contin labeling recommends that “a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.”

²⁴ FDA Drug Safety Communication: FDA has reviewed possible risks of pain medicine use during pregnancy. January 9, 2015. <http://www.fda.gov/Drugs/DrugSafety/ucm429117.htm>

²⁵ Draft Guidances for Industry: Analgesic Indications: Developing Drug and Biological Products (February 2014); and, Abuse Deterrent Opioids-Evaluation and Labeling (January 2013).

²⁶ Leyla Sahin, MD, Amy Taylor, MD, MHS. Citizen Petition and Petition for Stay regarding Neonatal Opioid Withdrawal Syndrome (NOWS) labeling changes. April 11, 2014. DARRTS Reference ID: 3488324

²⁷ FDA Drug Safety Communication: FDA has reviewed possible risks of pain medicine use during pregnancy. January 9, 2015. <http://www.fda.gov/Drugs/DrugSafety/ucm429117.htm>

²⁸ MS Contin (morphine sulfate) labeling. Drugs@FDA. Accessed 9/12/2016.

Clinical Trial Findings Arymo ER

The applicant did not conduct studies with Arymo ER in lactating women, and there were no reported cases of women who breastfed during clinical trials with Arymo ER.

Applicant's Review of Published Literature

Egalet US Inc. performed a literature search in Embase and Medline from 1987 to March 31, 2016 using the search terms “morphine and lactation/breastfeeding.” and reviewed several published articles including the following:

- A lactation study of five lactating women who underwent surgery at least one month after giving birth and were given either a lumbar epidural blockage with morphine or general anesthesia (given morphine intravenously (IV) or intramuscularly (IM) as needed). The milk: plasma (M/P) ratio averaged 2.45.²⁹
- In a case report, a woman was treated with intrathecal morphine pump during pregnancy and post-partum for the treatment of complex regional pain syndrome. Breast milk samples were taken daily for the first seven weeks of life and maternal serum and breast milk morphine levels were taken on 10 separate occasions between weeks one and seven. Levels in milk were undetectable in 8 of the 11 samples. In 3 of the 11 samples, morphine was detected, but only at levels below the quantification sensitivity of the assay and was not related to maternal dose. The infant's post-partum course was uncomplicated.³⁰
- In a randomized prospective study, 102 pregnant women who underwent cesarean section were randomly assigned to receive either PCA morphine or PCA meperidine after surgery. The authors noted that infants in the morphine group were significantly more alert and oriented to animate human auditory cues than infants in the meperidine group.³¹

The reader is referred to the applicant's “Summary of Clinical Safety Addendum-Pregnancy and Lactation Labeling Rule” document for further details of the studies reviewed.³²

The applicant's review of published literature was inadequate, and DPMH conducted a more comprehensive review of literature related to morphine use during lactation in the section below.

DPMH's Review of Published Literature

DPMH performed a search of *Medications and Mother's Milk*³³, Micromedex³⁴, the Drugs and Lactation Database (LactMed)²⁶ and PubMed using the search terms “morphine and lactation” and “morphine and breastfeeding”. In addition to the published literature reviewed

²⁹ Feilberg, et al. Excretion of morphine in human breast milk. *Acta Anaesthesiol Scand*. 1989 Jul;33(5):426-8.

³⁰ Oberlander, et al. Prenatal and breast milk morphine exposure following maternal intrathecal morphine treatment. *J Hum Lact*. 2000 May;16(2):137-42.

³¹ Wittels, et al. Post-cesarean analgesia with both epidural morphine and intravenous patient-controlled analgesia: neurobehavioral outcomes among nursing neonates. *Anesth Analg*. 1997; 85(3): 600-6.

³² EDR 2.7.4. Egalet US Inc. Clinical Safety Addendum-Pregnancy and Lactation Labeling Rule

³³ Hale, Thomas, Ph.D. *Medications and Mother's Milk: A Manual of Lactational Pharmacology*-2012, 15th edition. Hale Publishing, L.P.

³⁴ <http://www.micromedexsolutions.com/micromedex2/librarian/PFDefaultActionId/evidencexpert.DoIntegratedSearch#>

by the applicant, DPMH reviewed additional published studies. The results of the literature search are described below.

In *Medications and Mother's Milk*, Dr. Thomas Hale, a breastfeeding expert, notes that morphine is present in breastmilk and that infants under one month of age have a prolonged elimination half-life and decreased clearance of morphine relative to older infants. Although a relative infant dose of 9.1% has been calculated in published articles, Dr. Hale notes that morphine has poor oral bioavailability and "is probably the preferred opiate in breastfeeding mothers." However, high doses of morphine over prolonged periods of time may result in sedation and respiratory depression in infants.

Micromedex notes the following:

"Infant risk cannot be ruled out. Available evidence and/or expert consensus are inconclusive or are inadequate for determining infant risk when used during breastfeeding. Although the American Academy of Pediatrics and World Health Organization state that therapeutic doses of morphine can usually be administered safely during the breastfeeding period, because of the possibility of excess sedation and respiratory depression in the nursing infant, morphine sulfate is not recommended for the nursing mother."

LactMed states the following:

"Epidural morphine given to mothers for post-cesarean section analgesia results in trivial amounts of morphine in their colostrum and milk. Intravenous or oral doses of maternal morphine in the immediate postpartum period result in higher milk levels than with epidural morphine. Labor pain medication may delay the onset of lactation. Maternal use of oral narcotics during breastfeeding can cause infant drowsiness, central nervous system depression and even death. Newborn infants seem to be particularly sensitive to the effects of even small dosages of narcotic analgesics. Once the mother's milk comes in, it is best to provide pain control with a nonnarcotic analgesic and limit maternal intake of morphine to a few days at a low dosage with close infant monitoring. If the baby shows signs of increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness, a physician should be contacted immediately."

In addition, LactMed provided a summary of the following clinical lactation studies and case reports. The information that follows was summarized in LactMed but additional details about the studies have been added after a review of the published articles by DPMH.

- In a clinical lactation study, six women who received epidural morphine 5 mg for labor analgesia had their initial colostrum sampled postpartum (range 24-100 hours after epidural). Morphine was undetectable (<0.6 mcg/L) in four of the women. The peak morphine level was 4.5 mcg/L and was measured 28 hours after the epidural dose. The authors of LactMed noted that considering the small amount of colostrum consumed by the infant and based on the peak level in this study, an exclusively

breastfed infant would only receive a negligible amount of morphine from a maternal epidural 5 mg morphine dose for labor analgesia.³⁵

- In a non-randomized lactation study (Wittels, *et al.*) of ten mother-infant pairs who had undergone cesarean section delivery at term, five mothers received a loading dose of IV meperidine after umbilical cord clamping and then received patient-controlled analgesia (PCA) with IV meperidine, and finally meperidine tablets as needed. Five mothers were given IV morphine 7.5 mg after umbilical cord clamping and then 1 to 1.5 mg every 6 minutes via intravenous (PCA) as needed for up to 48 hours postpartum. When PCA morphine was discontinued, oral morphine 5 to 30 mg every two to three hours as needed was given. Colostrum and milk were sampled from each of the mothers six times (at 12, 24, 26, 48, 72 and 96 hours) over 96 hours postpartum. Average milk levels from all the mothers studied were about 50 to 65 mcg/L in the first 48 hours postpartum and then dropped to about 20 mcg/L by 72 to 96 hours postpartum. The average cumulative IV only dose in the first 48 hours postpartum was about 150 mg. The average cumulative IV plus oral morphine dose over the entire 96 hours was about 250 mg. Using the average milk levels reported at each of the six collection times from this study, an exclusively breastfed infant would receive about 5 mcg/kg daily. Using the maximum level of 65 mcg/L reported in the first 48 hours postpartum when mothers were receiving IV morphine, and assuming 30% oral absorption by the infant, an exclusively breastfed infant would absorb a maximum of about 3 mcg/kg daily equal to 0.3% of the IV maternal weight-adjusted daily dosage. A blinded psychologist evaluated each infant on day of life three with the Brazelton Neonatal Behavioral Assessment Scale (NBAS). Four outcomes were used (alertness, visual orientation, auditory orientation, and visual/auditory orientation) and infants in the morphine group scored higher and were more alert and oriented ($p < 0.05$) than infants in the meperidine group. The authors determined that morphine provided equivalent maternal analgesia to meperidine but with less neurobehavioral depression in breastfed infants.³⁶
- In a case report (Robieux, *et al.*), a mother who had been receiving daily morphine (50mg orally every 6 hours) during the third trimester for back pain due to Systemic Lupus Erythematosus stopped morphine one week after delivery but was restarted five days later due to withdrawal effects in the mother. The mother was breastfeeding her infant, and the reported concentration of morphine in the foremilk and hindmilk was 100ng/ml and 10ng/ml, respectively. The authors estimated that the relative infant dose was 0.8 to 12% of the maternal oral dose and noted that infant had normal behavior, weight gain and sleeping patterns and breastfeeding was continued.³⁷

³⁵Bernstein J, et al. Colostrum morphine concentrations following epidural administration. *Anesth Analg.* 1989;68:S23.

³⁶ Wittels B, Scott DT, Sinatra RS. Exogenous opioids in human breast milk and acute neonatal neurobehavior: a preliminary study. *Anesthesiology.* 1990;73:864-9.

³⁷ Robieux, et al. Morphine excretion in breast milk and resultant exposure of a nursing infant. *J Clin Toxicol.* 1990;28:365-70.

Reviewer comment:

Dr. Hale reviewed this article in Medications and Mother's Milk and noted that the authors calculated the infant dose from the highest milk concentration and a milk intake of 150ml/kg/day. Therefore, the dose of morphine to the infant was probably lower.

- In a maternal pharmacokinetic (PK) study (Zakowski, *et al.*), 30 women were given epidural morphine (5 mg) immediately following cesarean section and again 24 hours later. Maternal plasma, breast milk, maternal and neonatal urine concentrations of unconjugated (UM) and conjugated (CM) morphine were measured in patients. Maternal blood samples (n=10) were collected at 0, 0.25, 0.5, 1, 2, 3, 4, 6, 12, and 24 hours after each dose and maternal urine was collected for three consecutive 24-hour periods (n=30). Breast milk samples (n=30) and neonatal urine samples (n=20) were collected. Serum, urine, breast milk UM and CM levels were measured using radioimmunoassay and PK values were calculated using non-compartmental analysis. There were measurable colostrum morphine levels 12 to 36 hours after delivery in only three of the women (range 0.39 to 0.66 mcg/L). The remaining 27 women had undetectable (<0.12 mcg/L) morphine milk levels. Maternal serum UM remained 40–50% higher, and CM 50–100% higher in the first hour following dose two than the respective values after dose one ($P < 0.05$). Values for area under the curve (AUC), AUMC, $T_{1/2}$, and MRT increased 28%, 83%, 35% and 36%, respectively, with the second dose ($P < 0.05$), while CI decreased 19% ($P < 0.05$) with no significant difference in V_{ss} . Total urinary excretion of morphine decreased significantly from 1.98 ± 0.15 mg on day 1 to 1.6 ± 0.2 mg and 0.19 ± 0.002 mg on days 2 and 3, respectively ($P < 0.01$). Breast milk and neonatal urine contained negligible amounts of morphine, signifying minimal neonatal transfer.³⁸
- In a clinical lactation study (Baka, *et al.*), seven women who had preterm infants (31 weeks $\pm$ 0.9 weeks) delivered by cesarean section were started on IV morphine 7 to 10 mg over 30 to 60 minutes, then 1 mg every 10 minutes by patient-controlled analgesia (PCA) as needed, for up to 48 hours postpartum. Colostrum samples were taken just prior to PCA initiation and again at 12, 24, 36, and 48 hours postpartum. The average cumulative morphine dose was about 60 mg in 48 hours. Three of the women could not produce enough milk for sampling. Morphine and its active metabolite, M6G, were detectable in three of the remaining four women. There was high inter-subject variability with peak milk levels occurring at different times and a wide range of levels measured in each of the women. The peak milk morphine level was 48 mcg/L and the peak 6-glucuronide metabolite level was 1,084 mcg/L. The authors reported median morphine levels of 34, 24, 7, 6.5 and 21 mcg/L and M6G levels of 273, 672, 426, 527 and 350 mcg/L at 0, 12, 24, 36 and 48 hours, respectively. Using the reported median milk levels from the 60 mg cumulative 48 hour maternal morphine dose in this study, an exclusively breastfed infant would receive 2.4 mcg/kg daily of morphine and 73 mcg/kg daily of the 6-glucuronide metabolite. Using the peak milk level data from this study, an exclusively breastfed

³⁸ Zakowski MI, Ramanathan S, Turndorf H. A two-dose epidural morphine regimen in cesarean section patients: pharmacokinetic profile. *Acta Anaesthesiol Scand.* 1993;37:584-9.

infant would receive an estimated maximum of 7.2 mcg/kg daily of morphine and 163 mcg/kg daily of the M6G. The authors concluded that the morphine and M6G concentrations found in breast milk are very small in nursing mothers receiving IV morphine via PCA after cesarean delivery and that neonatal uptake does not seem to be significant. The authors concluded that mothers receiving routine doses of morphine via PCA after cesarean delivery should be allowed to breast-feed.³⁹

- In a lactation study (Guo, *et al.*), 12 women who underwent cesarean section deliveries at 37 to 41 weeks of gestation received a single dose of morphine (2 mg) epidurally. Colostrum was collected at several times during the first 24 hours postpartum. The highest average morphine concentration was reported to be 6.2 mg/L and occurred in colostrum three hours after the cesarean section. The morphine concentration fell with an average half-life of three hours. By six hours after the dose, the reported concentration was 1.1 mg/L. By 24 hours, the drug was undetectable in colostrum. The authors of Lactmed noted that it is likely that this paper reported the milk concentration values in the wrong units. The values reported were probably in mcg/L, not mg/L.⁴⁰
- In a prospective study, 102 term parturients underwent cesarean section delivery and received epidural anesthesia. After umbilical cord clamping, each patient received epidural morphine (4mg) and was randomly assigned to receive either PCA meperidine or PCA morphine. The authors found that breastfed newborns of mothers using intravenous PCA morphine for post-cesarean analgesia were more alert and better oriented after postpartum day 3 than infants of mothers using intravenous PCA meperidine. There was no difference in newborn respiratory rates.⁴¹
- In an observational study, 390 infants were born to opioid-dependent women undergoing treatment during pregnancy (methadone (n=184), buprenorphine (n=77), slow-release morphine (n=129). Compared to infants who were not breastfed (n = 91), breastfed infants (n = 21) had lower average measures of neonatal abstinence, lower dosage requirements of morphine (5.23 mg vs 8.75 mg), shorter durations of treatment for neonatal abstinence (10.2 vs 18.1 days) and shorter hospital stays (19.7 vs 31 days).⁴²

³⁹ Baka, et al. Colostrum morphine concentrations during postcesarean intravenous patient-controlled analgesia. *Anesth Analg.* 2002;94:184-7.

⁴⁰ Guo, et al. Study on pharmacokinetics of morphine in the latex of lying-in women after PCA. *Chin Pharm J (China)*. 2008;43:127-8.

⁴¹ Wittels B, Glosten B et al. Postcesarean analgesia with both epidural morphine and intravenous patient-controlled analgesia: neurobehavioral outcomes among nursing neonates. *Anesth Analg.* 1997;85:600-6.

⁴² Metz VE, Comer SD, Pribasniig A et al. Observational study in an outpatient clinic specializing in treating opioid-dependent pregnant women: Neonatal abstinence syndrome in infants exposed to methadone-, buprenorphine- and slow-release oral morphine. *Heroin Addict Relat Clin Probl.* 2015;17:5-15.

- Morphine can increase serum prolactin.⁴³ However, the prolactin level in a mother with established lactation may not affect her ability to breastfeed.
- In an analysis of data from the 2005-2007 Infant Feeding Practices Study II (Lind, *et al.*), the authors conducted a longitudinal study of women from late pregnancy through 12 months postpartum to assess the relationship between the mother's use of labor pain medication and delayed onset of lactation (DOL) (milk coming in >3 days after delivery). Compared to women who delivered vaginally and received no labor pain medications, women who received labor pain medication had a higher odds of experiencing DOL⁴⁴:
 - Vaginal delivery with spinal/epidural: adjusted odds ratio (aOR) 2.05; 95% CI, 1.43-2.95
 - Vaginal with spinal/epidural plus another medication: aOR 1.70; 95% CI, 1.16-2.76
 - Vaginal with other labor pain medication only: aOR 2.13; 95% CI, 1.39-3.27
 - Planned cesarean with spinal/epidural plus another medication: aOR 2.67; 95% CI, 1.35-5.29
 - Emergency cesarean section with spinal/epidural only: aOR 2.17; 95% CI, 1.34-3.51
 - Emergency cesarean section with spinal/epidural plus another medication: aOR 3.03; 95% CI, 1.77-5.18

In the 2013 Clinical Report on the Transfer of Drugs and Therapeutics into Human Breast Milk, the American Academy of Pediatrics (AAP) noted that “when narcotic agents are needed to treat pain in the breastfeeding woman, agents [such as] morphine are preferred... Morphine appears to be tolerated by the breastfeeding infant... Clearance of morphine is decreased in infants younger than 1 month and approaches 80% of adult values by 6 months of age.”⁴⁵

Summary

Overall, morphine is present in human milk with milk/plasma (M/P) ratios ranging between 1.1 and 3.6 (based on AUC) and relative infant doses ranging between 0.8% and 12%. Since Arymo ER is an extended-release opioid product, Arymo ER labeling will be structured in the PLLR format using ER/LA opioid labeling.

Morphine and Females and Males of Reproductive Potential

Nonclinical Experience

No formal animal fertility studies have been conducted to assess the potential of morphine to impair fertility. There are nonclinical studies in published literature that have demonstrated adverse effects of morphine on male and female fertility (changes in hormonal levels,

⁴³ Tolis G, Dent R, Guyda H. Opiates, prolactin, and the dopamine receptor. *J Clin Endocrinol Metab.* 1978;47:200-3

⁴⁴ Lind JN, Perrine CG, Li R. Relationship between use of labor pain medications and delayed onset of lactation. *J Hum Lact.* 2014;30:167-73.

⁴⁵ Sachs HC. The Transfer of Drugs and Therapeutics Into Human Breast Milk: An Update on selected topics. *Pediatrics* 2013; 132(3).

including testosterone, luteinizing hormone, serum corticosterone, reduction in total pregnancies, higher incidence of pseudopregnancies, and reduction in implantation sites). The reader is referred to the Nonclinical review by Beth Bolan, Ph.D. for further details.

Applicant's Review of Published Literature

Egalet US Inc. performed a literature search in Embase and Medline from 1987 to March 31, 2016 using the search terms “morphine and sperm and fertility” and reviewed three studies^{46,47,48} that demonstrated reduced fertility in females and males of reproductive potential exposed to morphine.

Summary

Based on the conclusions reached by the Division of Bone, Reproductive and Urologic Products (DBRUP) in a 2014 review of literature to evaluate the association between chronic opioid administration and hypogonadism⁴⁹, DAAAP updated the immediate and extended release opioid labelings to include information about the potential for chronic opioid use to influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency. Section 8.3, Females and Males of Reproductive Potential, of opioid labeling will now include the following statement:

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

CONCLUSIONS

Arymo ER labeling has been updated to comply with the PLLR and has the following recommendations for Arymo ER labeling:

- **Warnings and Precautions, Section 5.3**
 - Based on the increased likelihood of adverse infant effects due clinical experience with morphine in pregnant women, a subsection describing embryo- and/or fetal risks (“Neonatal Opioid Withdrawal Syndrome”) as well as mitigation measures must be placed in the Warnings and Precautions section of labeling as required by regulation (21 CFR 201.57(c)(9)(i)(A)(4).
- **Pregnancy, Section 8.1**
 - The “Pregnancy” section of Arymo ER labeling was formatted in the PLLR format to include “Risk Summary,” “Clinical Considerations,” and “Data” sections.⁵⁰

⁴⁶ Smith CG, Gilbeau PM. Drug abuse effects on reproductive hormones. In: Thomas JA, Korach KS, McLachlan JA, editors. Endocrine Toxicology. New York, New York, USA. Raven Press, 1985. P. 249-67.

⁴⁷ Agirregoitia E, et al. Expression and localization of delta-, kappa-, and mu-opioid receptors in human spermatozoa and implications for sperm motility. J Clin Endocrinol Metab. 2006 Dec;91(12):4969-75.

⁴⁸ Agirregoitia E, et al. . Regulation of human sperm motility by opioid receptors. Andrologia. 2012 May;44 Suppl 1:578-85.

⁴⁹ DBRUP review of chronic opioid treatment and hypogonadism. September 29, 2014. DARRTS Reference ID 3649510.

⁵⁰ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

- **Lactation, Section 8.2**
 - The “Lactation” section of Arymo ER labeling was formatted in the PLLR format to include the “Risk Summary” and “Clinical Considerations” sections.⁵¹
- **Females and Males of Reproductive Potential, Section 8.3**
 - The “Females and Males of Reproductive Potential” section of Arymo ER labeling was formatted in the PLLR format to include the “Infertility” section to discuss the potential for chronic use of opioids to cause reduced fertility in females and males.⁵²
- **Patient Counseling Information, Section 17**
 - The “Patient Counseling Information” section of Arymo ER labeling was updated to correspond with changes made to sections 5.3, 8.1, 8.2 and 8.3 of labeling.

RECOMMENDATIONS

DPMH revised sections 5.3, 8.1, 8.2, 8.3 and 17 of Arymo ER labeling for compliance with the PLLR (see below). See Appendix A for the Applicant’s proposed labeling. DPMH refers to the final NDA action for final labeling.

⁵¹ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

⁵² Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, C-8.3 Females and Males of Reproductive Potential.

DPMH Proposed Arymo ER (morphine sulfate) extended-release Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

WARNING: NEONATAL OPIOID WITHDRAWAL SYNDROME

See full prescribing information for complete boxed warning.

- Prolonged use of ARYMO ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.3)

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

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

FULL PRESCRIBING INFORMATION

WARNING: NEONATAL OPIOID WITHDRAWAL SYNDROME

Neonatal Opioid Withdrawal Syndrome

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

5 WARNINGS AND PRECAUTIONS

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of ARYMO ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see *Use in Specific Populations* (8.1)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [see *Warnings and Precautions* (5.3), *Clinical Considerations*]. There are no available data with ARYMO ER in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. Published studies with morphine use during pregnancy have not reported a clear association with morphine and major birth defects [see *Data*]. In

animal reproduction studies, {Pharm/Tox to insert information} [see Data]. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/neonatal adverse reactions

(b) (4)

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset of neonatal withdrawal symptoms usually occurs in the first days after birth. The duration and severity of neonatal opioid withdrawal syndrome may vary. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly [see Warnings and Precautions (5.3)].

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid induced respiratory depression in the neonate. ARYMO ER is not recommended for use in women during and immediately prior to labor, when shorter acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including ARYMO ER, can prolong labor through actions that temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor.

Data

Human Data

The results from a population-based prospective cohort, including 70 women exposed to morphine during the first trimester of pregnancy and 448 women exposed to morphine at any time during pregnancy, indicate no increased risk for congenital malformations. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and non-randomized study design.

Animal Data

(b) (4)

8.2 Lactation

Risk Summary

Morphine is present in breast milk. Published lactation studies report variable concentrations of morphine in breast milk with administration of immediate-release morphine to nursing mothers in the early postpartum period with a milk-to-plasma morphine AUC ratio of 2.5:1 measured in one lactation study. However, there is insufficient information to determine the effects of morphine on the breastfed infant and the effects of morphine on milk production. Lactation studies have not been conducted with extended –release morphine, including ARYMO ER. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with ARYMO ER.

Clinical Considerations

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

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [*see Adverse Reactions (6.2), Clinical Pharmacology (12.2), Nonclinical Pharmacology (13.1)*].

17 PATIENT COUNSELING INFORMATION

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of ARYMO ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [*see Warnings and Precautions (5.3), Use in Specific Populations (8.1)*].

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that ARYMO ER can cause fetal harm and to inform the prescriber of a known or suspected pregnancy [*see Use in Specific Populations (8.1)*].

Lactation

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

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible [*see Use in Specific Populations (8.3)*].

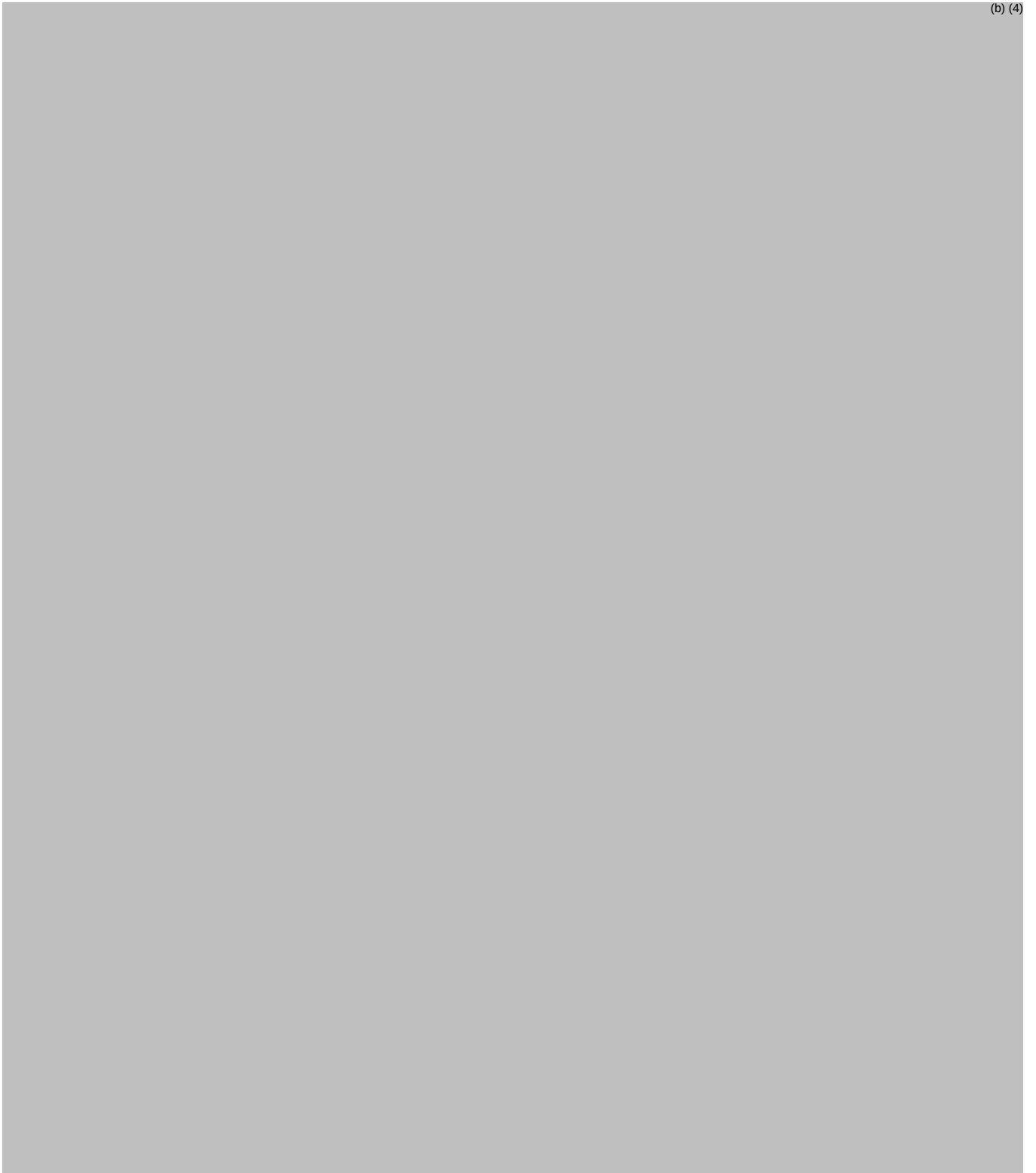
MEDICATION GUIDE

Tell your healthcare provider if you are:

- pregnant or planning to become pregnant.** Prolonged use of ARYMO ER during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- breastfeeding.** Not recommended during treatment with ARYMO ER. It may harm your baby.

**APPENDIX A – Applicant’s Proposed Arymo ER (morphine sulfate) extended-release
Pregnancy and Lactation Labeling**

(b) (4)



4 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS)
immediately following this page

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

/s/

MIRIAM C DINATALE
09/23/2016

LYNNE P YAO
09/28/2016



MEMORANDUM

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

Date: August 15, 2016

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

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

From: James M. Tolliver, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Arymo ER (Morphine Sulfate) Extended-Release Tablets, EG-001 Tables, NDA 208-603
Trade Name, dosages, formulations, routes: 15 mg, 30 mg, and 60 mg morphine sulfate tablets intended for oral administration.
IND Number: 117,317
Indication(s): Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Sponsor: Egalet US Inc.
PDUFA Goal Date: October 14, 2016

Materials Reviewed:

Abuse-related preclinical and clinical data in NDA 208-603, (SN 0001), submission date: December 14, 2015).Additional materials

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I. SUMMARY

1. Background

This memorandum responds to a consult request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) to evaluate from an abuse-deterrent perspective data submitted by Egalet US Inc. under NDA 208-603 for Arymo ER (Morphine Sulfate) Extended-Release Tablets, also known as EG-001 Tablets. This product is formulated as a tablet with dosage strengths of 15 mg, 30 mg, and 60 mg morphine sulfate intended for oral administration. EG-001 Tablets is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. EG-001 tablets have not previously been marketed in the U.S. or other countries. As a product containing morphine sulfate, EG-001 tablets are in Schedule II of the Federal Controlled Substances Act (CSA)

2. Conclusions

1. Overall Conclusions: Data submitted under NDA 208-603 provides support for deterrent claims for EG-001 to abuse by insufflation and intravenous injection, but not to oral administration. The results of Category 3 intranasal human abuse potential (HAP) study 067-EG-009 demonstrate a potential deterrent effect of EG-001 to insufflation. Difficulty in reducing the particle size of EG-001 Tablets as evidenced by Category 1 physical manipulation studies provide additional support for a deterrent effect to insufflation. Results of Category 1 syringeability/injectability studies indicate a potential deterrent effect of EG-001 to intravenous abuse. Based on the results of Category 3 oral HAP study 067-EG-008, EG-001 tablets does not appear to have a deterrent effect to oral abuse.
2. In HAP study 067-EG-008, oral manipulated MS Contin 60 mg (control) produced a mean Emax of Drug Liking of 73.3 mm which was statistically significantly greater ($p=0.0385$) than that produced by oral manipulated EG-001 60 mg (68.3 mm). The median times to achieve Emax (TEmax) were 1.02 and 1.99 hours for manipulated MS Contin and manipulated EG-001, respectively, although the mean Drug Liking time course profile suggests that much of the rise in Drug Liking occurred with 1.5 hours following ingestion of manipulated EG001. The clinical relevance of the 5 mm difference in Drug Liking VAS between oral manipulated MS Contin and oral manipulated EG-001 with respect to a possible oral abuse deterrent effect is not known.

3. Results from HAP study 067-EG-008 do not support a potential deterrent effect of EG-001 to oral abuse. In HAP study 067-EG-008, statistical examination of responder analysis revealed that 50% of the completer population (38 subjects) did not display a 5% or greater reduction in Emax of Drug Liking following manipulated EG-001 60 mg compared to following manipulated MS Contin 60 mg.
4. In HAP study 067-EG-008, oral manipulated MS Contin 60 mg produced a mean Emax of High (51.9 mm) that was statistically significantly higher ($p=0.0175$) than that produced by oral manipulated EG-001 60 mg (38.8 mm). The median times to Emax of High were 1.5 and 3.0 hours for manipulated MS Contin 60 mg and manipulated EG-001 60 mg, respectively. Mean High time effect profile demonstrates a plateau of High which is mostly reached within 1.5 to 2 hours, following ingestion with manipulated EG-001.
5. In HAP study 067-EG-008, with respect to Take Drug Again, the Emax produced by oral manipulated MS Contin 60 mg (70.1 mm) was not statistically significantly different ($p=0.0967$) from that produced by oral manipulated EG-001 60 mg (62.9 mm). This does not support a possible deterrent effect of EG-001 to oral abuse.
6. In HAP study 067-EG-008, oral administration of manipulated EG-001 60 mg produced a mean Emax of Overall Drug Liking (65.1 mm) that was not statistically significantly different ($p=0.226$) from that produced by oral manipulated MS Contin 60 mg (69.8 mm). This does not support a deterrent effect of EG-001 to oral abuse.
7. In HAP study 067-EG-008, relative bioavailability analyses for plasma morphine conducted by Sponsor using least square mean ratios and 90% confidence intervals showed that treatment with manipulated EG-001 60 mg produced a lower Cmax (28.74 ng/mL) of plasma morphine compared to treatment with manipulated MS Contin 60 mg (Cmax = 42.34 ng/mL). The calculated times to Cmax (Tmax) were 0.88 and 2.12 hours for manipulated MS Contin 60 mg and manipulated EG-001 60 mg, respectively.
8. In intranasal HAP study 067-EG-009, intranasal EG-001 high volume and intranasal EG-001 60 mg low volume produced mean Emax scores of Drug Liking of 65.5 mm and 59.6 mm, respectively, that were statistically significantly lower ($p<0.0001$) than the mean Emax of Drug Liking produced by intranasal MS Contin 60 mg (77.7 mm). The median times to achieve Emax of Drug Liking were 1.01, 1.75, and 1.01 hours for intranasal MS Contin and intranasal high volume and low volume EG-001, respectively.
9. In intranasal HAP study 067-EG-009, the mean Emax of intranasal MS Contin 60 mg (61.2 mm) was statistically significantly ($p<0.0001$) higher than that produced by either high volume (27.7 mm) or low volume (16.0 mm) intranasal EG-001 60 mg. The median times to achieve Emax of High were 2.00, 2.01, and 0.75 hours for the intranasal administration of MS Contin 60 mg, high volume EG001, and low volume EG-001 60 mg, respectively.
10. In intranasal HAP study 067-EG-009, treatment with intranasal MS Contin 60 mg resulted in a mean Take Drug Again Emax of 69.9 mm which was statistically significantly ($p<0.0001$) higher than that observed following intranasal EG-001 60 mg high or low volume (43.1 mm and 52.6 mm, respectively).

11. In intranasal HAP study 067-EG-009, with respect to Overall Drug Liking, the mean Emax produced by intranasal MS Contin 60 mg was statistically significantly ($p < 0.0001$) higher than that produced by intranasal low volume and high volume EG-001 60 mg (54.4 mm and 53.9 mm, respectively).
12. Intranasal MS Contin was associated with a higher mean morphine maximum plasma level (Cmax) of 36.3 ng/mL compared to either intranasal high volume EG-001 (19.02 ng/mL) or intranasal low volume EG-001 60 mg (4.77 ng/mL). Median time to achieve Cmax for plasma morphine was shorter for intranasal MS Contin (1.13 hours) compared to high or low volumes of EG-001 (2.17 and 2.66 hours, respectively).
13. For the Ease of Snorting VAS, only the intranasal EG-001 60 mg high volume treatment had a low mean score within the “difficult” range of the scale (mean of 17.0 mm out of 100 mm). Mean scores for all other treatments were in the “easy” range of the scale and within 5 points of each other (range of mean scores 73.8 mm to 78.0 mm).
14. For intranasal treatments including MS Contin, EG-001 low volume, and placebo, the mean maximum scores were less than 1 for all six nasal symptoms, indicating at most mild nasal adverse effects resulting from these treatments. Following intranasal EG-001 high volume, mean maximum subjective nasal scores for “need to blow nose”, “nasal congestion”, “intranasal irritation”, and “nasal congestion” were 2.1, 2.1, 1.5, and 1.3, respectively, indicating some mild-to-moderate nasal effects.
15. Category 1 studies demonstrate that EG-001 tablets are difficult to physically manipulate using available household tools. These tablets can be cut into numerous pieces (i.e., 2, 4, 8, 16, and 32 pieces). Of the household tools evaluated, the spice grinder was determined to be most efficient in reducing the particle size of EG-001 tablets, although approximately 75% by weight of the particles were greater than 1000 microns in size. The difficulty in reducing the particle size provides additional evidence of a potential deterrent effect of EG-001 tablets to intranasal abuse. In contrast to what is found with EG-001, MS Contin tablets, the positive control, can be reduced to a fine powder using a mortar and pestle.
16. Category 1 large volume (200 mL) extraction studies demonstrate that with cutting of EG Tablets into pieces using a knife or grinding of EG tablets using a spice grinder the controlled release properties for morphine from tablets is compromised, as indicated by elevated rates of morphine extraction using tap water and other solvents. Extractions with hot water and other heated solvents also can compromise the controlled release of morphine, resulting in rapid extraction of morphine from EG-001 tablets. These studies suggest a potential susceptibility of EG-001 tablets to manipulation with oral abuse. (See Figures 2, 3, and 4 as well as Table 2 in Discussion)
17. Category 1 dissolution studies conducted on EG-001 tablets cut (Chef’s knife) into 2, 4, 8, 16, and 32 pieces, demonstrate that with each increase in number of EG-001 tablet pieces, there is a concomitant increase in the rate of release of morphine into the dissolution media, reflecting greater compromise in the controlled release of morphine. These studies suggest a potential susceptibility of EG-001 tablets to manipulation with oral abuse. (See Figure 1 of Discussion)

18. The results of Category 1 injectability/syringeability studies support an abuse deterrent claim for EG-001 with regard to abuse by intravenous injection. With use of 2, 5, or 10 mL of tap water, it is difficult to prepare suitable intravenous solutions using intact, cut, or ground EG-001 60 mg tablets due to such factors as low recovery of fluid, increased fluid viscosity, and low recovery of morphine. By contrast, placement of a single ground tablet of the positive control, 60 mg MS Contin, in 2 mL or 5 mL of tap water for 10 minutes resulted in solutions of sufficient volume with little viscosity and containing concentrations of morphine likely to produce subjective reinforcing effects. (See Tables 3 and 4 of Discussion)
19. Under the conditions utilized by Sponsor in a simulated smoking study, EG-001 60 mg tablet ground when heated resulted in less than 3.1% LC of morphine recovered in vapor suggest that under the conditions utilized EG001 tablets cannot be smoked. At the same time, the Sponsor did not evaluate the positive control, MS Contin, for possible abuse by smoking. In the absence of assessing the comparator, no abuse deterrent claim can be given to EG-001 tablets regarding abuse by smoking.

3. Recommendations

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

1. Consideration should be given to allowing abuse deterrent claims for EG-001 Tablets with respect to abuse by intravenous injection. The Category 1 injectability/syringeability studies demonstrated that it was difficult to produce suitable intravenous solutions using EG-001 tablets. At the same time, these studies demonstrated that the positive control, MS Contin, could be readily used to produce intravenous solutions.
2. Consideration should be given to allowing abuse deterrent claims for EG-001 Tablets with respect to abuse by snorting (insufflation). Category 1 physical manipulation studies demonstrated that with use of available household tools it was difficult to crush/ground EG-001 tablets, whereas MS Contin tablets could be easily ground into a fine powder. Category 3 intranasal HAP study 067-EG-009 demonstrated that the insufflation of ground EG-001 was associated with statistically significant, lower maximum scores for Drug Liking VAS, High VAS, Take Drug Again VAS, and Overall Drug Liking VAS compared to that produced by the insufflation of the positive control, ground MS Contin.
3. Consideration should be given to not allowing abuse deterrent claims for EG-001 Tablets with respect to oral abuse. In oral HAP study 067-EG-008, although the Emax of Drug Liking is statistically significantly lower following oral manipulated 60 mg EG-001 compared to following oral manipulated 60 mg MS Contin (positive control), this difference is small and of questionable clinical relevance. Subjects expressed a similar willingness to take again, if given the opportunity either oral manipulated 60 mg EG-001 or oral manipulated 60 mg MS Contin as revealed by Take Drug Again VAS. With use of the Overall Drug Liking VAS, subjects displayed a similar drug liking experience when given either of the oral manipulated treatments. (b)(4)
4. Consideration should be given to not granting a deterrent claim to EG-001 Tablets with respect to smoking. Although the in vitro data suggests that EG-001 tablets may not likely be smoked,

Sponsor did not conduct similar simulated smoking studies on the positive control, MS Contin, to determine the likelihood it might be abused by smoking. (b) (4)

II. DISCUSSION

1. Chemistry

1.1 Substance Information

EG-001 tablets intended for oral administration are formulated for extended release of morphine sulfate at dosage strengths of 15 mg, 30 mg, and 60 mg morphine sulfate. The quantitative compositions of EG-001 tablets for all dosage strengths are provided in Table 1 below.

Polyethylene oxide is a commonly used release controlling excipient in abuse-deterrent products and comprises (b) (4)% of the EG-001 matrix tablet composition, (b) (4). The drug release from the EG-001 tablet is controlled by erosion of the polyethylene oxide tablet matrix (b) (4) thereby extending the drug release. EG-001 tablets are produced using a hot-melt extrusion process resulting in a hard tablet.

Table 1. Composition of To-Be-Marketed EG-001 Tablets.

Component	Dosage Strengths of EG-001 Tablets			Function
	15 mg	30 mg	60 mg	
	Mg per Tablet (%)	Mg per Tablet (%)	Mg per Tablet (%)	
Morphine Sulfate	15.00 (1.98)	30.00 (3.94)	60.00 (7.83)	Drug Substance
Polyethylene Oxide 400,000 (b) (4)	(b) (4)			Release controlling; Abuse-Deterrent properties (b) (4)
Butylated Hydroxytoluene (b) (4)	(b) (4)			
Total Weight	759.21 (100.0)	761.69 (100.00)	766.53 (100.00)	----

Polyethylene oxide is a commonly used release controlling excipient in abuse-deterrent products and comprises (b) (4) % of the EG-001 matrix tablet composition, (b) (4). The drug release from the EG-001 tablet is controlled by erosion of the polyethylene oxide tablet matrix (b) (4) thereby extending the drug release. EG-001 tablets are produced using a hot-melt extrusion process resulting in a hard tablet.

(b) (4)

1.3 In Vitro Manipulation and Extraction Studies for Products with Abuse-Deterrent Features

EG-001 Tablets are formulated using Egalet's proprietary Guardian™ Technology consisting of a polymer matrix formed utilizing plastic injection molding methodology. According to Sponsor, this formulation is intended to be hard making it difficult to chew, resist particle size reduction, and block attempts at chemical extraction of morphine sulfate. In addition, the presence of the PEO is intended to result in a viscous hydrogel on contact with liquid, making syringeability difficult.

The following study reports from (b) (4) constitute the Category 1 studies conducted for the EG-001 formulation.

- (b) (4) Study Number: (b) (4) AD001 entitled Egalet's Morphine PR Abuse-Deterrent Study - Interim (Category 1 – Phase I Study) Report
- (b) (4) Study Number (b) (4) AD001 entitled Egalet's Morphine PR Abuse-Deterrent Study – Final Report (Category 1 – Phase II Study).
- (b) (4) Study Number (b) (4) AD003 entitled “Egalet's Morphine PR (EG-001) Category 1 Abuse-Deterrent PII Supplemental Study”
- (b) (4) Study Number (b) (4) AD004 entitled “In Vitro Laboratory Abuse-Deterrent Studies of Egalet's EG-01 (Abuse-Deterrent, Extended-release Morphine Sulfate) Tablets, 10 mg – To Be Marketed Product (TBMP)

An additional 274 page report intended to summarize the relevant data from the four (b) (4) reports was also provided and is entitled “Appendix 1: Expert Review and Data Interpretation of Category 1 In Vitro Laboratory Assessment of Egalet 001, an Abuse-Deterrent, Extended-Release, Oral Morphine-Based Product.

It should be noted that much of the Category 1 data was generated on an EG-001 100 mg tablet that does not constitute a to-be-marketed formulation. The data generated with this 100 mg tablet is not discussed in this review. Instead, this review will focus on the to-be-marketed 60 mg EG-001 tablet formulation. Some work was also conducted on the 15 mg and 30 mg strengths of EG-001; however, the results generated from the 60 mg dosage strength are representative of those results generated from the 60 mg dosage strength.

According to Sponsor, the Category 1 studies described in this report were designed and conducted in accordance with the 2015 final Food and Drug Administration Guidance (April, 2015, Guidance for Industry Abuse-Deterrent Opioids-Evaluation and Labeling).

MS Contin was used as the positive control in the Category 1 studies. Sponsor specifically noted in a submission to NDA 208603 dated June 3, 2016 that no other positive controls, other than MS Contin, were used in the Category 1 studies.

Physical Manipulation

Physical manipulation studies demonstrated that EG-001 tablets (60 mg) are difficult to manipulate using a variety of household tools. By contrast, MS Contin tablets (100 mg) was readily reduced in particle size by most of these same tools.

The following tools were examined for particle size reduction of EG001 tablets and MS Contin Tablets: spoons, mortar & pestle, hammer, foot file, food grater, knife, razor blade, pill crusher, coffee grinder, and spice grinder. Particle size of resulting manipulated samples was determined using sieve analyses.

Of these tools, spoons, mortar & pestle, hammer, and pill crushed produced 0% weight of EG-001 particles with a particle size of <1000 microns. The foot file, food grater, and razor blade produced less than 5% weight of EG-001 particles with a size <1000 microns. Of the remaining tools, manipulation of EG-001 tablets using the spice grinder, coffee grinder, and knife resulted in 5.8%, 6.8%, and 10.3% of particle weight with a size of <1000 microns. Pre-treatment of EG-001 tablets by heating (microwave for 3 minutes or oven - 100°C for 30 minutes) or cooling (freezer -20°C for 1 hour) had no effect on particle size reduction.

With the exception of the hammer, all tools produced greater than 66% weight of particles of MS Contin < 1000 microns.

Optimal methods used for particle size reduction utilized the mortar & pestle for MS Contin and the spice grinder for EG-001.

- For EG-001 Tablets - A pulsing procedure for operating the spice grinder (15 seconds of grinding followed by a 15 second rest period for a total grinding time of 2.5 minutes) incurred less instrument failure than with longer grinding times (and less failure than with the coffee grinder). Pre-cutting EG-001 into 4 pieces before grinding enhanced the reproducibility of the method. With this method approximately 20% of particles were < 1000 microns. Consequently, this procedure was adopted as the “optimal method” for grinding EG-001 and was used in all subsequent experiments (extractions, syringeability, and simulated smoking studies) involving ground EG-001.
- For MS Contin Tablets - 20 seconds in a mortar and pestle produced a consistent fine ground material with ~55% of particles <500 microns. This method was used for manipulated MS Contin used in the Category 1 large volume extractions and intravenous injection studies.

Dissolution Study Using Manipulated (Cut) EG-001 60 mg Tablets

Sponsor submitted to NDA 208603 (DARRTS, eCTD 19) on July 20, 2016, data for a dissolution study conducted on manipulated (cutting into pieces) EG-001 60 mg tablets (to-be-marketed formulation).

Sponsor evaluated the release of morphine as a function of the number of pieces into which EG-001 60mg to-be-marketed tablets were cut. The dissolution media consisted of 0.1 N HCl. Using a chef's knife, EG-001 tablets were cut into 2, 4, 8, 16, and 32 pieces. The rates of release of morphine from

intact and manipulated samples were determined over the range of 45 minutes to 630 minutes. The results are provided in Figure 1 below.

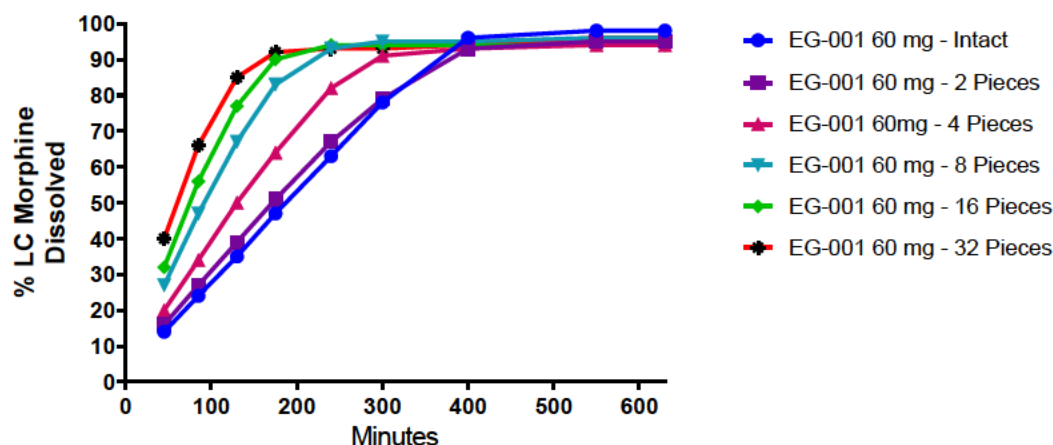


Figure 1. Dissolution Study in 0.1N HCl Demonstrating the Percent Label Claim of Morphine Recovered as a Function of Time from EG-001 60 mg Tablets Intact as well as Cut into 2, 4, 8, 16, and 32 Pieces. (N =3 or 2). (Source: Sponsor Submission eCTD 19, July 20, 2016)

Figure 1 shows that as the number of pieces of EG-001 60 mg increases over the range from 4 pieces to 32 pieces, there is a corresponding increase in the %LC of morphine released. As EG-001 tablets are cut into increasing number of pieces, there is a concomitant increase in surface area associated with an increase in rate of release of morphine.

Large Volume Chemical Extraction Studies

Extractability studies were conducted using a variety of solvents with different characteristics (aqueous, organic, protic, aprotic, and acid/basic). Solvents included tap water, saline, 0.1M HCl, vinegar, pH buffers (2, 4, 6, and 8), 20% ethanol, 50% ethanol, 95% ethanol, methanol, isopropanol, acetone, ethyl acetate, hexane, and methylene chloride. Solvents were used at a volume of 200 mL at either room temperature (RT) or at elevated temperature (90°C or 60°C).

Extractions were carried out on intact, cut, and ground EG-001 60 mg tablets. Cut samples consisted of 32 pieces obtained using a Chef's knife. Ground EG-001 samples were acquired using the "optimal method" mentioned above with use of a Spice grinder.

Figure 2 demonstrated the effects of particle size reduction and solvent temperature on the rate of extraction (recovery) of morphine from intact and manipulated (cut into 32 pieces and ground) EG-001 tablets. With a reduction in particle size as seen when moving from intact to cut to ground there was a corresponding increase in the rate of morphine recovery, particularly evident over the first hour of extraction. At the one hour extraction time point, approximately 15%, 44%, and 65% recovery of morphine was achieved from intact, cut, and ground EG-001 60 mg tablets, respectively. Also evident from Figure 1 was the increase in the initial rate of morphine recovery (first 30 minutes) from intact and cut EG-001 tablets following an increase in temperature of the tap water to 90°C. Due to the already existing rapid increase in rate of recovery of morphine resulting just from grounding the EG-001, little additional rate increase was obtained by also increase the temperature of the tap water. The results

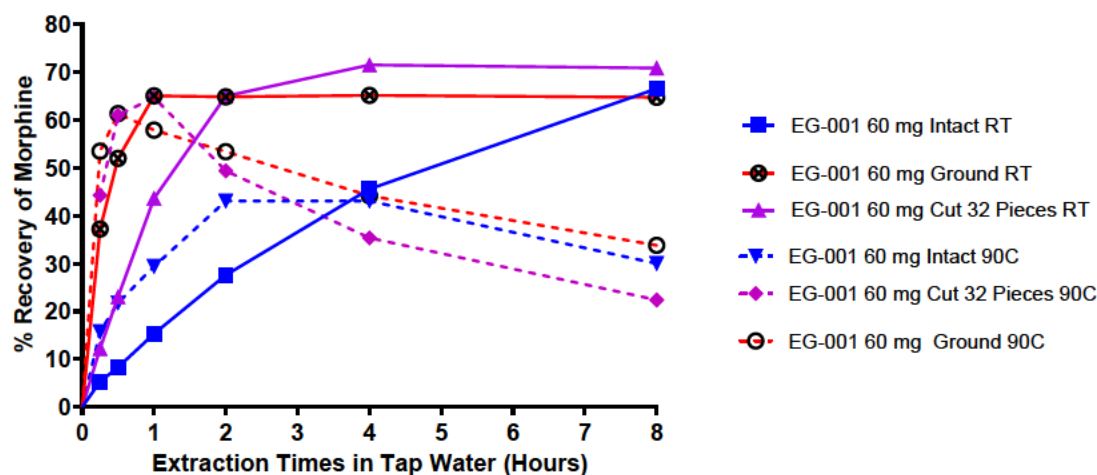


Figure 2. Mean Percentage Recovery of Morphine from Intact (Blue), Cut (32 pieces) (Purple), and Ground (Red) EG-001 Tablets as a Function of Time Following Exposure to 200 mL of Tap Water Held at Room Temperature (RT) (Solid Lines) or 90°C (Dashed Lines). (N=3)

indicate that the controlled release of morphine from EG-001 tablets can be compromised by either increasing the particle size or by increasing solvent temperature, in this case the temperature of tap water. For reasons that are not clear, with exposure to tap water at elevated temperature, there was an initial rapid increase in rate of morphine release over the first 2 hours and a fall in morphine levels over the subsequent 2 to 8 hour time points.

Figure 3 demonstrates the extraction of morphine over the first 8 hours from intact EG-001 tablets using different solvents. The bold blue line represents the extraction time course using tap water. For most of the solvents, the time course of morphine extraction was similar to that observed for tap water. With use of 50% ethanol and 95% ethanol there was some reduction in the rate of morphine extraction. For all solvents morphine extraction was less than 10% at 15 minutes and less than 25% at 30 minutes.

Figure 4 below shows extraction of morphine from ground EG-001 tablets. With use of each of these solvents there was an increase in the rate of extraction of morphine from ground EG-001 tablets compared to intact EG-001 tablets (compare Figure 3 to Figure 4). At 30 minutes, less than 25% extraction of morphine was extracted from intact tablets (see Figure 3). At the same time point using ground tablets (Figure 4), the extraction ranged from 39% (for 95% ethanol) to about 78% (for pH 4 buffer). With each of the solvents utilized morphine was extracted from either intact or ground EG-001 60 mg tablets. With grinding, there is further compromise of the extended release properties of EG-001 60 mg tablets.

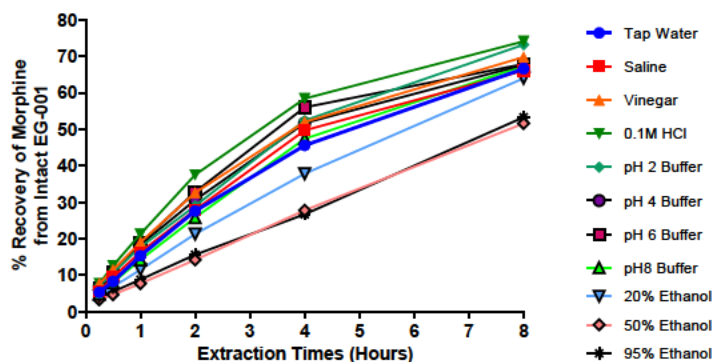


Figure 3. Mean Extraction of Morphine from Intact EG-001 Tablets as a Function of Time with Exposure to 200 mL of Selected Solvents at Room Temperature and With Stirring. (N = 3) (Note the bold blue line representing tap water.) (Data Source: (b) (4) Study Number: (b) (4) AD003)

Additional solvents evaluated for extraction of morphine from intact and ground EG-001 60 mg tablets and as reported in (b) (4) Study Number (b) (4) AD003 included methanol, isopropanol, acetone, ethyl acetate, methylene chloride, and hexane. Methanol and methylene chloride showed some extraction of morphine from intact EG-001 tablets, which was further increased with use of ground tablets. Isopropanol, acetone, ethyl acetate, and hexane were not generally effective in the extraction of morphine from EG-001 tablets 60 mg.

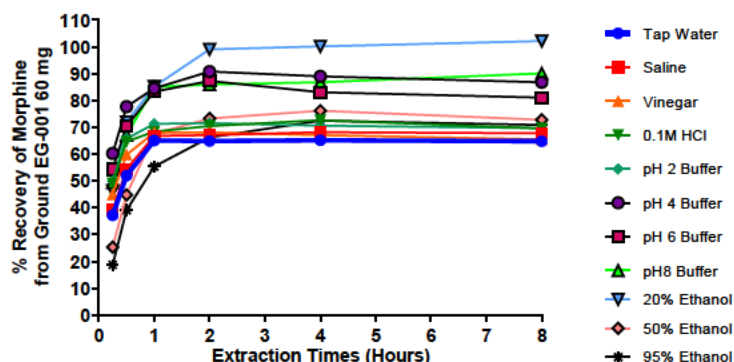


Figure 4. Mean Extraction of Morphine from Ground EG-001 Tablets as a Function of Time with Exposure to 200 mL of Selected Solvents at Room Temperature and With Stirring. (N = 3) (Note the bold blue line with solid circles representing tap water.) (Data Source: (b) (4) Study Number: (b) (4) -AD003)

Table 2 below provides data from (b) (4) Study Number: (b) (4) AD004 regarding extraction of morphine as a function of time from EG-001 60 mg tablets that have been cut with a knife into 32 pieces. The solvents examined are the ones assessed above for extraction of morphine from intact and ground tablets. Solvents such as tap water, saline, 0.1M HCl, vinegar, pH buffers (2, 4, 6, and 8), 20% ethanol, and 50% ethanol are effective in the extraction of morphine from cut EG-001 tablets. When the temperature of each of these solvents is increased, there is an increase in the rate of morphine extraction observed over the first 2 hours. With use of 95% ethanol, methanol, isopropanol, acetone, ethyl acetate, hexane, and methylene chloride as solvents, morphine extraction was assessed with solvents held at just

room temperature. For these solvents, with the exception of methylene chloride, extraction of morphine from cut EG-001 60 mg tablets was limited.

Table 2. Extraction of Morphine from Cut (32 Pieces) EG-001 60 mg Tablets In Various Solvents Held at Room Temperature and Elevated Temperature. (Data from (b) (4) Study Number: (b) (4))

Solvent	Solvent Temperature	Average % Recovery Of Morphine from One 60 mg EG-001 Tablet Cut Into 32 Pieces As A Function of Extraction Time (N = 3)						
		0.083 hrs	0.25 hrs	0.5 hr	1 hr	2 hrs	4 hrs	8 hrs
Tap Water	RT	5.47	12.21	23.04	43.64	65.02	71.53	70.89
	90C	15.24	44.31	61.01	64.76	49.41	35.35	22.40
Saline	RT	7.03	15.08	26.37	48.82	70.06	77.72	80.84
	90C	19.35	53.06	75.47	86.22	83.11	82.78	77.87
Vinegar	RT	9.21	16.66	27.22	47.40	71.26	75.46	73.79
	90C	21.4	55.86	72.42	77.84	76.00	73.07	65.50
0.1M HCl	RT	8.17	16.53	27.47	47.41	71.45	78.48	78.34
	90C	19.68	57.75	79.10	84.48	81.20	81.36	75.81
pH2 Buffer	RT	7.18	14.70	25.03	42.16	65.09	63.30	71.60
	90C	17.19	45.30	64.84	68.33	69.15	63.97	43.68
pH 4 Buffer	RT	6.84	14.20	23.92	46.95	64.00	67.08	65.82
	90C	13.87	40.75	64.96	70.44	70.05	71.34	72.28
pH 6 Buffer	RT	7.16	14.35	25.04	43.22	67.40	70.84	71.17
	90C	14.74	43.82	63.72	73.32	71.28	73.52	73.65
pH 8 Buffer	RT	4.86	12.58	22.96	46.34	57.30	71.98	76.27
	90C	11.19	34.38	54.34	70.53	73.04	66.82	67.57
pH 10 Buffer	RT	3.09	8.75	20.21	41.76	59.13	68.67	71.84
	90C	6.13	23.06	50.51	69.40	67.22	63.34	50.13
20% Ethanol	RT	3.31	8.29	14.48	26.62	47.87	68.03	72.06
	60C	9.77	26.54	48.40	66.57	71.31	71.64	68.09
50% Ethanol	RT	2.87	6.32	11.47	22.64	41.98	67.68	79.64
	60C	8.87	25.45	52.80	77.57	83.80	78.14	78.87
95% Ethanol	RT	0.00	2.10	2.86	4.55	6.67	10.61	16.02
Methanol	RT	3.96	6.11	8.16	12.07	17.52	24.52	34.33
Isopropanol	RT	0.00	0.00	0.00	0.00	2.68	4.26	7.08
Acetone	RT	0.00	0.00	0.00	3.54	5.73	8.69	12.48
Methylene Chloride	RT	5.22	23.81	43.49	66.35	57.93	61.81	65.19
Ethyl Acetate	RT	0.00	0.00	0.00	0.00	2.96	5.04	8.04
Hexane	RT	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Syringeability Studies Using Small Volumes

The results of the extractability/syringeability studies indicate that the positive control, MS Contin, but not EG-001, can be easily used to make suitable intravenous solutions. It is possible that with 24 hour extraction of EG-001 intact or manipulated in tap water or 3% saline, solutions recovered may upon intravenous injection result in some reinforcing subjective effects. Overall, the data indicates that EG-001 tablets may provide an abuse deterrent effect to intravenous abuse when compared to MS Contin.

Extractability and syringeability studies were conducted to evaluate the use of MS Contin and EG-001 tablets for producing solutions suitable for abuse by intravenous injection. As part of the review of these studies, the HAP study by Stoops et al. (2010)¹ will be used. Using a double-blind, within-subject, randomized, placebo-controlled study design, Stoops et al. (2010) examined the subjective effects of intravenous injection of morphine sulfate (5 mg, 10 mg, and 20 mg) on subjective effects, including Drug Liking (visual analog scale), in non-dependent, recreational opioid users with a history of intravenous opioid use. Intravenous injection of 5 mg, 10 mg or 20 mg of morphine sulfate produced levels of drug liking that were significantly above that produced by placebo. These data suggest that a solution suitable for intravenous injection should contain at least 5 mg of morphine sulfate, which is likely to produce sufficient reinforcing effects such as drug liking. For purposes of this review and based on the results from Stoops et al., (2010), a suitable intravenous solution is one that upon injection can deliver 5 mg or more of morphine intravenously in a limited volume, preferably 1 milliliter or less.

Studies examined in this review utilized single to-be-marketed 60 mg EG-001 tablets, with the comparator being single 60 mg MS Contin. Intact, cut, and ground EG-001 tablets were used. EG-001 60 mg tablets were ground using the Spice grinder. MS Contin tablets were ground using a mortar and pestle.

Studies were conducted using 2, 5, and 10 mL of tap water held at either room temperature or at 90°C with extraction periods of 5, 10, and 30 minutes. Extraction out to 30 minutes did not substantially increase the recovery of morphine over that seen at 10 minutes. As such, for this review, the 10 minute extraction time point was used. Extractability was assessed by determining the percentage label claim of morphine recovered. Syringeability was assessed by attempting to pass any given solution through needles ranging in size from 18 to 27 gauges.

As can be seen from Table 3, the positive comparator, 60 mg MS Contin could be readily used to produce a suitable intravenous solution. Placement of a ground 60 mg MS Contin tablet in just 2 mL of tap water held at room temperature for 10 minutes, followed by passage through a small bore 27 gauge needle resulted in 1.6 mL of recovered solution containing 26.7 mg of morphine (concentration of 16.69 mg/mL). Based on the results of Stoops et al (2010) just 0.5 mL of this solution might be expected to produce significant levels of Drug Liking. With use of 5 mL and 10 mL of tap water, there was a further increase in the amount of morphine recovered (approximately 34-35 mg) as well as in the recovered volume (4.4 and 9.5 mL, respectively) resulting in lower final solution morphine concentrations (7.73 mg/mL starting from 5 mL tap water and 3.78 mg/mL from starting with 10 mL of tap water.). In the case of the 7.73 mg/mL solution injection of 1 mL or less might produce Drug Liking. On the other hand it may require more than 1 mL of the 3.78 mg/mL solution to produce subjective effects. Also as evident from Table 2, with increases in solvent temperature to 90°C, there was some limited increase in the recovery of morphine and morphine concentration making the resulting solutions suitable for intravenous injection.

¹ Stoops WW, Hatton KW, Lofwall MR, Nuzzo PA, and Walsh SL (2010). Intravenous oxycodone, hydrocodone, and morphine in recreational opioid users: abuse potential and relative potencies. *Psychopharmacology*, 212 (2): 193-203.

Table 3. Preparation of Solutions Suitable for Intravenous Injection Using Ground MS Contin and Ground EG-001 60 mg Tablets in Selected Volumes (2, 5, or 10 mL) of Tap Water. (N = 3) (Data from (b) (4) Study Number (b) (4) AD004)

Drug - Single Tablet	Initial Volume of Tap Water	Needle gauge	Average Volume Ejected	Average % Recovery Of Morphine	Average Mg of Morphine Recovered	Concentration of Morphine mg/mL
Tap Water – Room Temperature – 10 minutes						
Ground 60 mg MS Contin	2	27	1.6	44.5	26.7	16.69
	5	27	4.4	56.7	34.02	7.73
	10	27	9.5	59.8	35.88	3.78
Ground 60 mg EG-001	2	27	0.20	1.1	0.66	3.3
	5	18	2.2	7.2	4.32	1.96
	10	27	8.0	9.3	5.58	0.69
Tap Water – 90 C – 10 minutes						
Ground 60 mg MS Contin	2	27	1.73	66.5	39.9	23.06
	5	27	4.80	73.6	44.16	9.2
	10	27	9.83	71.7	43.02	4.38
Ground 60 mg EG-001	2	N/A	N/A	N/A	N/A	N/A
	5	27	0.73	2.7	1.62	2.22
	10	27	6.17	18.5	11.1	1.80

In contrast to what was found using MS Contin, with the use of a single ground 60 mg EG-001 tablet it was not possible to produce a suitable intravenous solution under the conditions stipulated in Table 2 above. When starting with 2 mL of tap water either at room temperature or 90°C there was little recovery of solution (< 0.2 mL) at 10 minutes of extraction. With starting volumes of 5 mL and 10 mL tap water, the recovery of solution tended to be limited with the total extraction of morphine less than 5.6 mg resulting in low morphine concentrations (range 0.69 mg/mL to 2.2 mg/mL). With the low recovery of morphine, it is not likely that the resulting solutions upon intravenous injection would produce subjective reinforcing effects.

Table 4 below provides the results of studies in which intact, cut, and ground EG-001 tablets are extracted for 4 hours and 24 hours in 5 mL of either tap water or 3% saline. Extraction of intact or manipulated (cut or ground) EG-001 60 mg tablets for 4 hours in either solvent held at room temperature did not result in any solutions suitable for intravenous injection. There was too little morphine extracted from each of the samples.

With extraction extended out to 24 hours under room temperature conditions, several resulting solutions upon i.v. injection might produce some limited reinforcing effects. So, for example, 24 hour extraction of cut 60 mg EG-001 in tap water resulted in a solution of 1.73 mL containing 9.8 mg of morphine for a concentration of 5.67 mg/mL. This solution required an 18 gauge needle for ejection thereby indicating that it most likely had an increased viscosity. Likewise, 24 hour extraction of the intact 60 mg EG-001 resulted in 2.87 milliliters of solution having a morphine concentration of 3.87 mg/mL. More than more milliliter of such a solution, intravenously injected might produce some subjective effects. This would also hold true for extraction of ground 60 mg EG-001 for 24 hours using 3% saline resulting in a final morphine concentration of 4.69 mg/mL. In this case the viscosity appears of have been lower since the solution was ejected using a 27 gauge needle.

Table 4. Use of Extended Extraction Times (4 hours and 24 hours) For Producing Suitable Intravenous Solutions from Intact and Manipulated EG-001 Tablets Using 5 mL of Tap Water or Saline. (N=3) (Data from (b) (4) Study Number (b) (4) AD004)

Solvent	Intact or Manipulated	Needle gauge	Average Milliliters Ejected	Average % LC Recovery Morphine	Average Mgs of Morphine Recovered	Morphine Concentration mg/mL
EG-001 – 5 mL - Room Temperature – 4 hours						
Tap Water	Intact	27	3.93	5.0	3.0	0.76
	Cut	27	2.40	4.9	2.9	0.59
	Ground	27	1.80	4.7	2.8	1.56
3% Saline	Intact	27	4.00	4.9	2.9	0.59
	Cut	18	2.53	4.8	2.9	0.61
	Ground	27	1.80	2.2	1.3	0.59
EG-001 – 90 C – 5 mL – Room Temperature - 24 minutes						
Tap Water	Intact	18	2.87	18.5	11.1	3.87
	Cut	18	1.73	16.3	9.8	5.67
	Ground	N/A	N/A	N/A	N/A	N/A
3% Saline	Intact	18	1.20	7.4	4.4	3.67
	Cut	18	1.33	9.0	5.4	4.06
	Ground	27	2.07	16.1	9.7	4.69

Isolation of Free-Base Morphine - pH Mediated Precipitation

Sponsor conducted a study to determine if free-base morphine could be precipitated from solutions of EG-001 by pH adjustments. This study was conducted because in comparison to the salt forms of opioids, the free base forms of opioids are generally more volatile and less subject to degradation. Sponsor noted that “Although most individuals who attempt to smoke opioids do so directly with the existing formulation, it is plausible that attempts will be made to isolate the free-base form for Smoking.”

Sponsor did not evaluate any comparator such as MS Contin for possible recovery of free-base morphine using pH mediated precipitation. In the absence of assessing the positive comparator, this study does not have relevance to potential abuse deterrent effects of EG-001 to abuse by smoking.

(b) (4)

Prior to conducting studies on EG-001, optimization of the precipitation procedure was established by use of a “morphine sulfate standard.” This procedure allowed isolation of a mean of 57% (adjusted for molecular weight) of the morphine as free base. The individual determinations (triplicate) were 55.3, 70.0, and 46.0%. Approximately 21% of the morphine remained dissolved in the solution. This procedure was applied in attempts to precipitate morphine free base from solutions of EG-001. It should be noted that the optimized procedure developed using the “morphine sulfate standard” does not represent an optimized procedure for obtaining the freebase of morphine from EG-001 tablets. Suffice it to note, this procedure did not work to obtain morphine freebase from EG-001 tablets due to the high viscosity of the solution preventing the precipitation of any free base.

Simulated Smoking Study

The objective of the simulated smoking study was to determine the potential of EG-001 Tablets to be abused by smoking. In this study, MS Contin was not evaluated; there was no positive control. Overall the results of this study indicate that under the simulated conditions utilized, EG-001 tablets cannot be abused by smoking. At the same time, however, it is not known whether, under the same conditions, MS Contin tablets may or may not be smoked. In the absence of the positive control, MS Contin, abuse deterrent claims for EG-001 Tablets with respect to smoking cannot be made.

For this study, a device was constructed to allow air passage over the heated formulation in the vaporization chamber. Vaporized or aerosolized morphine was captured in a vapor trap (cold finger). Following heating, the collector was removed and trapped morphine (amount volatilized) was assayed for drug content. For mass balance assessment, the heated residue was also analyzed for morphine to determine the amount remaining in the residue and/or lost due to degradation. Reference control materials, morphine base, and pure morphine sulfate were initially tested to determine temperature and heating times that were optimal conditions for morphine vaporization.

Simulated smoking studies of EG-001 were conducted in the smoking apparatus at predetermined, near optimum heating conditions (heating temperature and time length of heating) for vaporization of morphine (260°C, 280°C, and 300°C for 15 minutes). A separate experiment was conducted with directly applied heat to the test tube containing physically manipulated EG-001 (heated with a Sterno burner for 15 minutes or complete charring).

There was very low recovery of morphine from the vapors following heating of EG-001 tablets. A single physically manipulated EG-001 60 mg tablet at 260°C, 280°C, and 300°C and over an open flame for 15 minutes resulted in 1.6%, 2.3%, 2.7%, and 3.0% recovery of morphine from the resulting vapor. The average %recoveries of residual morphine that remained were as follows: 260°C, 52.7%; 280°C, 45.3%; 300°C, 36.5%; and Sterno heat, 23.2%. With increasing heat, there was clear evidence of morphine pyrolysis. These results suggest that using the methods described in this study EG-001 tablets cannot not be abused by smoking.

4. Clinical Studies

4.1 Human Abuse Potential Studies

In support of NDA 208603 the following two human abuse potential studies were conducted:

- Study 067-EG-008 entitled “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.” Study was conducted by PRA Health Sciences, Salt Lake City, UT between July and November 2014.
- Study 067-EG-009 entitled “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.” Study was conducted by PRA Health Sciences, Salt Lake City, UT between December 2014 and March 2015.

On January 28, 2016 CSS provided a consult to the CDER Office of Biostatistics requesting statistical reviews be conducted on pharmacodynamic measures from studies 067-EG-008 and 067-EG-009. The statistical reviews of both studies were finalized on July 12, 2016 (DARRTS, NDA 208603, July 12, 2016, Author: Wei Liu Ph.D.).

Oral Study 067-EG-008

Study 067-EG-008 was a single-center, randomized, double-blind, triple-dummy, 4-way crossover study having a Screening Visit, a Qualification Phase, a Treatment Phase (comprising 4 treatment periods, each of which included a 3 day/2 night in-clinic visit), and a Follow-up Visit. The primary objective was to compare the relative abuse potential of oral intact and oral manipulated formulations of EG-001 vs. oral manipulated MS CONTIN.

The secondary objectives of this study were:

- To determine the relationship between pharmacokinetic (PK) and pharmacodynamic (PD) parameters of oral manipulated Egalet PR morphine; and
- To assess the safety and PK of intact and manipulated formulations of Egalet PR morphine following oral administration.

An exploratory objective of this study included the evaluation of the relative abuse potential of oral Egalet PR morphine when manipulated and administered mixed in juice. This was conducted on 12 subjects who completed the main study. Due to the limited number of subjects (12) and to the uncertainty of how they were selected, the review will not will not examine this exploratory study.

Completer population consisted of 38 non-dependent recreational opioid users who had used opioids for non-medical purposes (i.e., for psychoactive effects) on at least 10 occasions within the last year and at least once in the 12 weeks before the Screening Visit. Subjects were required to pass the naloxone challenge test to show they were non-dependent to opioids.

In order to advance to the Treatment Phase, subjects were required to discriminate between oral 30 mg immediate release morphine and placebo during the Drug Discrimination Phase using the bipolar 0-100 point Drug Liking VAS based on the following criteria:

- Peak effect (Emax) score of ≥ 65 points for Drug Liking in response to morphine, and
- ≥ 15 -point Emax difference between morphine and placebo treatments during the first 2 hours following drug administration, and
- Placebo response ≥ 40 and ≤ 60 points for Drug Liking during the first 2 hours following drug administration.

During the Treatment Phase, subjects were randomized in a 1:1:1:1 ratio, where each subject received in a triple-dummy design all study treatments separated by a minimum 5-day washout period as indicated below:

- EG 001, 60 mg oral intact

- EG 001, 60 mg oral manipulated added directly to tongue
- MS CONTIN, 60 mg oral manipulated added directly to tongue
- Placebo

A triple-dummy design with corresponding placebo treatments relative to active drugs was used. Subjects swallowed an oral intact tablet (active or placebo), a manipulated (32 pieces) tablet of Egalet PR morphine (active or placebo), and a manipulated (crushed with a mortar and pestle) tablet of MS CONTIN (active or placebo). Each treatment was dispensed onto the tongue followed by several rinses with liquid not to exceed 240 mL.

According to Pharmacy Manual manipulation of EG-001 tablets was accomplished using a 7 inch Chef's knife, cutting board, and weight boat. On a cutting board, one EG-001 tablet was sliced into about 10 perpendicular cuts. Further cuts were made to the slices for a total of 3 minutes cutting time.

Methodology - Pharmacokinetics

For purposes of collecting pharmacokinetic data, blood samples were taken pre-dose and at 30 and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose. Various pharmacokinetic parameters for plasma morphine were conducted including, but not limited to the maximum observed plasma concentration (C_{max}) and the time to achieve C_{max} (T_{max}). Pharmacokinetic population consisted of 39 subjects.

Methodology – Pharmacodynamic Measures

Although Sponsor conducted a variety of pharmacodynamic measures, this review will focus of the primary endpoint of Drug Liking VAS, as well as on the secondary measures of High VAS, Take Drug Again VAS, and Overall Drug Liking VAS.

- Drug Liking VAS is scored using a 0-100 point bipolar VAS anchored in the center with a neutral anchor of "neither like nor dislike" (score of 50), on the left with "strong disliking" (score of 0) and on the right with "strong liking" (score of 100). Subjects responded to the statement "Do you like the drug effect you are feeling now?"
- High VAS was scored using a 0 to 100 point unipolar VAS anchored on the left by "not at all" (score of 0) and on the right by "extremely" (score of 100). Subjects responded to the statement "How High are you now?"
- Take Drug Again VAS was scored using a 0-100 point bipolar VAS anchored on the left with "definitely would not" (score of 0); "do not care" (score of 50); and anchored on the right with "definitely would" (score of 100). Subjects responded to the statement "Would you want to take the drug you just received again, if given the opportunity?"
- Overall Drug Liking VAS was scored using a 0 to 100 point bipolar VAS anchored on the left with "strong disliking" (score of 0); "neither like nor dislike" (score of 50) in the middle; and anchored on the right with "strong liking" (score of 100). Subjects responded to the statement "Overall, my liking for this drug is:"

Various pharmacodynamic parameters were calculated including, but not limited to, peak effect over the 24 hours of collection (E_{max}) and time to peak effect (T_{E_{max}}).

During Treatment Periods Drug Liking VAS and High VAS were collected at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose. High VAS was also administered pre-dose. Take Drug Again VAS and Overall Drug Liking VAS were administered at 12 and 24 hours post-dosing.

Results – Subject Disposition

A total of 78 subjects entered the study with all successfully completing the naloxone challenge test. Of the 78 subjects who entered the Drug Discrimination Phase, 34 did not meet the Drug Discrimination Test criteria and were withdrawn from the study, 4 subjects withdrew from the study themselves (Subjects 024 and 062 no longer wanted to participate in the study, Subject 093 withdrew for personal reasons and Subject 128 withdrew consent), and 1 subject (Subject 087) was discontinued due to an AE

Thirty-nine subjects met Drug Discrimination Test criteria, were randomized into the Treatment Phase and received at least 1 study treatment, thereby comprising the Safety population. One subject discontinued prior to completing all 4 treatment periods. Subject 008 withdrew consent after Treatment Period 1 and did not receive further treatments. In total, 38 subjects completed all 4 treatment periods and were included in the PD population. Thirty-nine subjects were included in the PK population.

Results – Pharmacokinetics of Morphine in Plasma

Both the C_{max} and T_{max} following oral treatments during the Treatment Phase are shown in Table 5.

Table 5. Descriptive Statistics for Plasma Morphine Pharmacokinetic Parameters by Treatment (PK Population (N=39) (Source: Table 11.4.2.2-1 from Clinical Study Report for Study 067-EG-008).

Morphine Plasma Pharmacokinetic Parameter	Statistic	Manipulated MS Contin 60mg (N=39)	Manipulated EG-001 60 mg (N=38)	Intact EG-001 60 mg (N=38)
C _{max} (ng/mL)	Mean (SD)	42.34 (14.31)	28.74 (9.09)	17.81 (6.60)
	Median	42.20	29.20	16.70
	Range	14.2, 79.0	12.5, 47.8	8.5, 32.3
	% CV	33.8	31.6	37.0
T _{max} (hours)	Median	0.880	2.120	4.120
	Range	0.63, 4.13	0.88, 4.15	1.63, 6.13

Relative bioavailability analyses for plasma morphine conducted by Sponsor using least square mean ratios and 90% confidence intervals showed that treatment with manipulated EG-001 60 mg produced a lower C_{max} (28.74 ng/mL) of plasma morphine compared to treatment with manipulated MS Contin 60 mg (C_{max} = 42.34 mg), but a higher plasma level of morphine than intact EG-001 60 mg (17.81 ng/mL). The calculated times to C_{max} (T_{max}) were 0.88, 2.12, and 4.12 hours for manipulated MS Contin, manipulated EG-001, and intact EG-001, respectively.

Results – Pharmacodynamic Measures

CDER Office of Biostatistics conducted statistical analyses for Drug Liking VAS, High VAS, Take Drug Again VAS, and Overall Drug Liking. Descriptive statistics provided by the Sponsor were verified as being accurate. Statistical tests on the primary and key secondary endpoints (n=38) were

conducted using the mixed effect model for pairwise treatment comparisons and Wilcoxon signed-rank test on the within-subject differences. Tests were 2-sided with an alpha of 0.05.

Responder analysis was conducted for Drug Liking VAS using criteria set forth in the April 2015 FDA Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling Document. Responders were categorized if they demonstrated at least 30%, 40%, or 50% reduction in Emax of Drug Liking. Binomial proportion was used to test the null hypothesis that 50% or fewer subjects were responders. This testing was conducted at a 2.5% significance level (1-sided).

Descriptive statistics and statistical analyses for all four measures are shown in Tables 6 and 7 respectively.

Table 6. Descriptive Statistics for Treatments in Treatment Phase for Completer Population (N=38). (Source: CDER Office of Biostatistics)

Measure	Statistics	Maximum Effect (Emax)			
		EG001 60 mg		Manipulated MS Contin 60 mg (n=38)	Placebo (n=38)
		Manipulated (n=38)	Intact (n=38)		
Bipolar Drug Liking VAS	Mean (SE)	68.3 (2.0)	63.2 (1.64)	73.3 (1.59)	53.3 (1.27)
	Median	67.0	62.0	74.0	50.0
	Q1,Q2	61, 75	56, 68	68, 79	50, 52
Unipolar High VAS	Mean (SE)	38.8 (4.15)	26.8 (3.97)	51.9 (3.83)	5.3 (1.87)
	Median	38.0	18.5	49.0	0
	Q1, Q2	18, 58	7, 47	34, 72	0, 1
Bipolar Take Drug Again VAS	Mean (SE)	62.9 (3.18)	54.8 (3.37)	70.1 (2.84)	51.0 (1.65)
	Median	61.5	56.0	68.0	50.0
	Q1, Q2	51, 71	50, 65	56, 80	50, 50
Bipolar Overall Drug Liking VAS	Mean (SE)	65.1 (3.02)	55.7 (3.21)	69.8 (2.50)	52.2 (1.31)
	Median	63.5	57.0	67.5	50.0
	Q1, Q2	51, 75	50, 66	57, 81	50, 50

Results – Drug Liking VAS

Drug Liking VAS is scored using a 0-100 point bipolar VAS anchored in the center with a neutral anchor of "neither like nor dislike" (score of 50), on the left with "strong disliking" (score of 0) and on the right with "strong liking" (score of 100). Subjects responded to the statement “Do you like the drug effect you are feeling now?”

Oral manipulated MS Contin produced a mean Emax of Drug Liking of 73.3 mm which was statistically significantly greater ($p=0.0385$) than that produced by oral manipulated EG-001 (68.3 mm) (See Tables 6 and 7). The median time to achieve Emax (TE_{max}) was 1.02 and 1.99 hours for manipulated MS

Table 7. Statistical Analysis (Two-Tailed) for Comparison Between Selected Treatments. (Completer Population N=38) (Source: CDER Office of Biostatistics).

Comparison	Mean Difference (SE)	95% CI	p-value
Bipolar Drug Liking VAS			
MS Contin Manipulated -Placebo	20.1 (1.8)	16.5, 23.8	<.0001
MS Contin Manipulated – EG001 Manipulated	5.0 (2.3)	0.3, 9.7	0.0385
Unipolar High VAS			
MS Contin Manipulated -Placebo	47.0 (4.1)	38.8, 55.2	<.0001
MS Contin Manipulated – EG001 Manipulated	13.3 (5.4)	2.4, 24.2	0.0175
Bipolar Take Drug Again VAS			
MS Contin Manipulated -Placebo	19.0 (3.4)	12.3, 25.8	<.0001
MS Contin Manipulated – EG001 Manipulated	7.2 (4.3)	-1.3, 15.7	0.0967
Overall Drug Liking VAS			
MS Contin Manipulated -Placebo	17.6 (2.8)	12.0, 23.2	<.0001
MS Contin Manipulated – EG001 Manipulated	4.7 (3.9)	-3.0, 12.5	0.226

Contin and manipulated EG-001, although the mean Drug Liking time course profile suggest that much of the rise in Drug Liking occurred with 1.5 hours following manipulated EG001 ingestion. The clinical relevance of the 5 mm difference in Drug Liking VAS between oral manipulated MS Contin and oral manipulated EG001 with respect to a possible abuse deterrent effect is not known.

Within the completer population of 38 subjects, 11 subjects had Emax of Drug Liking scores that were higher following EG-001 manipulated compared to MS Contin manipulated. Of the remaining subjects, 25 (65.79%), 21 (55.26%), 15 (39%), 14 (37%), 9 (24%), and 9 (24%) demonstrated $\geq 5\%$, $\geq 10\%$, $\geq 20\%$, $\geq 30\%$, $\geq 40\%$, and $\geq 50\%$ reductions, respectively, in Emax of Drug Liking following treatment with manipulated EG-001 compared to following treatment with manipulated MS Contin. Statistical analysis using the proportion test with 1-sided level of significance ($\alpha = 0.025$) demonstrated that a majority of subjects did not demonstrate a 5% or greater reduction in Emax of Drug Liking following EG-001 manipulated compared to MS Contin manipulated ($p = 0.0258$).

Results – High VAS

High VAS was scored using a 0 to 100 point unipolar VAS anchored on the left by “not at all” (score of 0) and on the right by “extremely” (score of 100). Subjects responded to the statement “How High are you now?”

Oral manipulated MS Contin produced a mean Emax of High (51.9 mm) that was statistically significantly higher ($p=0.0175$) than that produced by oral manipulated EG-001 (38.8 mm) (See Tables 6 and 7). The median times to Emax of High were 1.5 and 3.0 hours for manipulated MS Contin and manipulated EG-001, respectively. Mean High time effect profile demonstrates a plateau of High which is mostly reached within 0.75 and 1.5 hours, following ingestion of MS Contin and manipulated EG001, respectively.

Results – Take Drug Again VAS – 24 Hours

Take Drug Again VAS was scored using a 0-100 point bipolar VAS anchored on the left with “definitely would not” (score of 0); “do not care” (score of 50); and anchored on the right with “definitely would” (score of 100). Subjects responded to the statement “Would you want to take the drug you just received again, if given the opportunity?”

With respect to Take Drug Again, the Emax produced by oral manipulated MS Contin (70.1 mm) was not statistically significantly different ($p=0.0967$) from that produced by oral manipulated EG-001 (62.9 mm) (See Tables 6 and 7). As such, upon retrospective assessment of Take Drug Again after the drug effects had worn off (12 and 24 hours), subjects did not display a statistical difference in the degree of willingness to take again either oral manipulated EG-001 or oral manipulated MS Contin if given the opportunity to do so. This finding does not support an abuse deterrent effect of EG-001 to abuse by the oral route.

Results – Overall Drug Liking – 24 Hours

Overall Drug Liking VAS was scored using a 0 to 100 point bipolar VAS anchored on the left with “strong disliking” (score of 0); “neither like nor dislike” (score of 50) in the middle; and anchored on the right with “strong liking” (score of 100). Subjects responded to the statement “Overall, my liking for this drug is:”

Oral administration of manipulated EG-001 produced a mean Emax of Overall Drug Liking (65.1 mm) that was not statistically significantly different ($p=0.226$) from that produced by oral manipulated MS Contin (69.8 mm) (See Tables 6 and 7). As such, upon retrospective assessment of Drug Liking after the drug effects had worn off (12 and 24 hours), subjects did not observe a difference in the degree of Drug Liking following oral manipulated EG-001 compared to oral administration of manipulated MS Contin. This finding does not support an abuse deterrent effect of EG-001 to abuse by the oral route.

Intranasal Study 067-EG-009

Study 067-GE-009 was a single-center, randomized, double-blind, double-dummy, crossover study which included a Screening Visit, a Qualification Phase (Naloxone Challenge and Drug Discrimination Test), a Treatment Phase, and a Follow-Up Visit.

The primary objective was to compare the relative abuse potential of manipulated and manipulated/sieved EG001 to manipulated MS CONTIN when administered intranasally.

The secondary objectives of this study were:

- To determine the relationship between pharmacokinetic (PK) and pharmacodynamic (PD) parameters of manipulated and manipulated/sieved EG001 and manipulated MS CONTIN following intranasal administration;
- To assess the PK of manipulated and manipulated/sieved EG001 following intranasal administration; and

- To assess the safety of manipulated and manipulated/sieved EG001 following intranasal administration.

Subjects were non-dependent recreational opioid users with intranasal opioid insufflation experience.

In order to advance to the Treatment Phase subjects were required in the Drug Discrimination Test to discriminate between manipulated intranasal 30 mg immediate-release (IR) morphine and placebo. To prepare the 30 mg IR morphine treatment, commercially available 30 mg IR tablet was pulverized with a mortar and pestle. Placebo consisted of microcrystalline cellulose powder. The ability to discriminate was defined for Drug Liking on a bipolar 0-100 point visual analog scale (VAS) only, and was as follows, inclusive:

- Peak score (Emax) score of ≥ 65 points for Drug Liking in response to morphine, and
- ≥ 15 -point Emax difference between morphine and placebo treatments during the first 2 hours following drug administration, and
- Placebo response ≥ 40 and ≤ 60 points for Drug Liking during the first 2 hours following drug administration.

The Treatment Phase consisted of five treatment periods administered under fasted conditions with treatments separated by at least 5 days. All subjects received the manipulated intranasal EG001 treatment (high volume) in Treatment Period 1 in order to minimize any potential sequence effect. For the remaining 4 periods, consisting of low volume treatments the doses were administered in randomized, double-blind, double-dummy crossover manner such that all subjects received each of the treatments (1 per treatment day). The volume of the investigational products during the 4 latter treatment periods was standardized and the low-volume intranasal treatment (active drug or placebo) used in Treatments D (oral EG001) and E (placebo) was matched to the volume of Treatment B (manipulated/sieved EG001) and Treatment C (manipulated MS CONTIN) to ensure appropriate blinding of the study treatments. Descriptions of the treatments are provided in Table 8 below.

According to the Pharmacy Manual (Version 2.0, January 2015), manipulation of EG001 60 mg tablets and placebo EG001 tablets for both consisted of initially cutting each tablet into 4 pieces, following by grinding the pieces with a Spice Grinder (Waring Model #WSG30K) for 15 second intervals for a total grinding time of 2.5 minutes. The high volume treatment included all powder obtained including particle sizes above 1000 microns. For producing the low volume EG001 IN treatments, the resulting powder following grinding was passed through a 1000 micron mini sieve to remove all particles greater than 1000 microns. Manipulation of MS Contin for intranasal administration involved crushing 60 mg tablets with a glass pestle.

Subjects were instructed to complete study drug administration within 5 minutes; an additional 10 minutes was allowed if needed. If administration was not fully completed within 15 minutes, dosing was stopped and the amount (weight) not administered was recorded. Subjects who were unable to complete an intranasal administration were allowed to continue in the study. The amount of time needed for intranasal administration was recorded. For each treatment, the oral administration preceded the intranasal administration. Subjects were required to sit upright for 4 hours after each dose. Subjects were not allowed to blow their noses for 2 hours following dosing, and any episodes of sneezing within 1 hour were documented

Table 8. Treatments Administered During the Treatment Phase.

Treatment Designation	Treatment	Description of Treatment (As Obtained from Pharmacy Manual)
A	EG-001 60 mg IN High Volume	EG-001 60 mg manipulated IN high volume (including particle sizes greater than 1000 microns) + Placebo for EG001 60 mg Intact Oral.
B	EG-001 60 mg IN Low Volume	EG-001 60 mg manipulated/sieved IN low volume (only particles sized less than 1000 microns) + Placebo for EG001 60 mg Intact Oral
C	MS Contin 60 mg IN Low Volume	MS Contin 60 mg manipulated IN low volume + Placebo for EG-001 60 mg Intact Oral
D	EG-001 60 mg Intact Oral	EG-001 60 mg Intact Oral + Placebo EG001 manipulated IN low volume
E	Placebo IN	Placebo for MS Contin 60 mg manipulated IN low volume + Placebo for EG001 60 mg intact oral

Methodology – Pharmacokinetics of Plasma Morphine

For purposes of evaluating morphine plasma pharmacokinetics, blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, and 24 hours post-dose. For the purposes of this review the morphine plasma pharmacokinetic parameters of interest will include C_{max} and T_{max}.

Methodology – Pharmacodynamic Measures of Subjective Effects

In this study, bipolar Drug Liking VAS was the primary measure with E_{max} of Drug Liking being the primary endpoint. For the purposes of this review the secondary measures evaluated included unipolar High VAS, bipolar Take Drug Again VAS, and bipolar Overall Drug Liking VAS.

During Treatment Periods Drug Liking VAS and High VAS were collected at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose. High VAS was also assessed pre-dose. Take Drug Again VAS and Overall Drug Liking VAS were determined at 12 and 24 hours, post-dosing.

For purposes of this review the pharmacodynamic parameters of interest will include E_{max}, T_{E_{max}}, and AUE0-2hours

Methodology – Ease of Insufflation and Nasal Tolerability

A bipolar Ease of Snorting VAS, administered within 5 minutes following intranasal administration, was used for a subject rated assessment of the difficulty associated with snorting the various treatments. Subject rated nasal tolerability was determined using a Nasal Effects Assessment which was administered at 5, 15, 30, and 45 minutes and at 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose.

For purposes of evaluating morphine plasma pharmacokinetics, blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, and 24 hours post-dose. For the purposes of this review the morphine plasma pharmacokinetic parameters of interest will include C_{max}, T_{max}, and AUC0-2hours.

Results – Subject Disposition

A total of 83 subjects entered the study and underwent the Naloxone Challenge Test; 80 subjects passed the test and proceeded to the Drug Discrimination Test. Of the 80 subjects who entered the Drug Discrimination Test, 50 subjects completed the Drug Discrimination Test and 30 subjects discontinued prior to the Treatment Phase; 26 subjects failed the Drug Discrimination Test criteria, 1 subject withdrew from the study himself, 3 subjects withdrew due to adverse events

Fifty subjects met Drug Discrimination Test criteria, were randomized into the Treatment Phase and received at least 1 study treatment, thereby comprising the Safety population. In total, 46 subjects completed all 5 treatment periods and were included in the completers population. Four subjects discontinued prior to completing the study; 3 subjects withdrew from the study themselves (Subjects 053, 097 and 107) and 1 subject (Subject 034) discontinued for other reasons (positive breath alcohol test). The pharmacokinetic population consisted of 46 subjects.

Results – Morphine Plasma Pharmacokinetics

Both C_{max} and T_{max} for plasma morphine following treatments during the Treatment Phase are shown in Table 9 below. Intranasal MS Contin was associated with a higher mean morphine C_{max} of 36.3 ng/mL compared to either intranasal high volume EG001 (19.02 ng/mL) or intranasal low volume EG001 (4.77 ng/mL). Median T_{max} for plasma morphine was shorter for intranasal MS Contin (1.13 hours) compared to high or low volumes of EG001 (2.17 and 2.66 hours, respectively).

Table 9. Plasma Pharmacokinetics of Morphine Following Treatments.

Plasma PK Parameter for Morphine	Statistic	Intranasal MS Contin 60 mg (n = 37)	Intranasal EG001 60 mg High Volume (n = 45)	Intranasal EG001 60 mg Low Volume (n = 46)	Intact Oral EG001 60 mg (n = 39)
C _{max} (ng/mL)	Mean (SD)	36.33 (12.90)	19.02 (9.56)	4.47 (2.25)	17.20 (4.26)
	Median	34.60	19.80	4.08	18.10
	Range	6.5 – 62.3	4.2 – 40.1	1.0 – 11.3	9.3 – 24.8
T _{max} (h)	Median	1.13	2.17	2.66	3.65
	Range	0.42 – 2.67	1.13 – 6.13	0.85 – 6.10	1.13 – 6.17

Results – Pharmacodynamic Measures

CDER Office of Biostatistics conducted statistical analyses for Drug Liking VAS, High VAS, Take Drug Again VAS, and Overall Drug Liking. Descriptive statistics provided by the Sponsor were verified. Statistical tests on the primary and key secondary endpoints (n=46) were conducted using the mixed effect model for pairwise treatment comparisons and Wilcoxon signed-rank test on the within-subject differences.

Responder analysis was conducted for Drug Liking VAS using criteria set forth in the April 2015 FDA Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling Document. Responders were categorized if they demonstrated at least 30%, 40%, or 50% reduction in E_{max} of Drug Liking.

Descriptive statistics and statistical analyses for all four measures are shown in Tables 7 and 8 respectively.

Table 10. Descriptive Statistics for Pharmacodynamic Measures in Study 067-EG-009. (Completer Population = 46). (Source: CDER Office of Biostatistics)

Measures	Statistics	Treatments – Maximum Effect (Emax)				
		Intranasal EG001 60 mg High Volume (n=46)	Intranasal EG001 60 mg Low Volume (n=46)	Oral EG001 60 mg Intact (n=46)	Intranasal MS Contin 60 mg (n=46)	Placebo (n=46)
Bipolar Drug Liking VAS	Mean (SD)	65.5 (14.3)	59.6 (12.5)	68.5 (13.6)	77.7 (11.7)	54.7 (10.6)
	Median	62.0	52.5	68.0	77.5	51.0
	Q1,Q2	52, 76	51, 65	59, 77	70, 85	50, 58
Unipolar High VAS	Mean (SD)	27.7 (28.2)	16.0 (23.2)	36.7 (28.1)	61.2 (23.6)	10.7 (20.2)
	Median	20	5	34	65.5	0
	Q1, Q2	2, 50	0, 20	11, 52	42,79	0, 9
Bipolar Take Drug Again VAS	Mean (SD)	43.1 (29.6)	52.6 (17.2)	58.9 (24.9)	69.9 (27.4)	52.5 (12.7)
	Median	50.0	50.0	56.0	73.0	50.0
	Q1, Q2	19, 66	50, 58	45.75	57, 90	50, 51
Bipolar Overall Drug Liking VAS	Mean (SD)	53.9 (21.7)	54.4 (13.6)	59.4 (24.2)	72.7 (18.1)	52.1 (11.2)
	Median	51.0	50.5	59.0	71.0	50.0
	Q1, Q2	50, 67	50, 55	50, 77	61, 87	50, 51

Table 11. Summaries of Pair-Wise Comparisons for Pharmacodynamic Measures for Study 067-GE-009. (Completer Population = 46) (Source: CDER Office of Biostatistics)

Comparisons	Mean Difference (SE)	95% CI	p-value
Bipolar Drug Liking VAS			
MS Contin IN – Placebo IN	23.0 (2.1)	18.9, 27.2	<.0001
MS Contin IN – EG001 High Volume	12.2 (2.1)	7.9, 16.5	<.0001
MS Contin IN – EG001 Low Volume	18.1 (1.9)	14.3, 21.9	<.0001
Unipolar High VAS			
MS Contin IN – Placebo IN	50.5 (4.1)	42.3, 58.6	<.0001
MS Contin IN – EG001 High Volume	33.5 (4.5)	24.4, 42.6	<.0001
MS Contin IN – EG001 Low Volume	45.4 (3.8)	37.8, 52.9	<.0001
Bipolar Take Drug Again VAS			
MS Contin IN – Placebo IN	17.4 (4.0)	8.2, 26.5	<.0001
MS Contin IN – EG001 High Volume	26.7 (5.4)	14.4, 39.0	<.0001
MS Contin IN – EG001 Low Volume	17.3 (4.3)	7.3, 27.2	<.0001
Overall Drug Liking VAS			
MS Contin IN – Placebo IN	20.6 (2.9)	14.8, 26.3	<.0001
MS Contin IN – EG001 High Volume	18.8 (3.7)	11.3, 26.3	<.0001
MS Contin IN – EG001 Low Volume	18.2 (2.9)	12.4, 24.1	<.0001

Results – Bipolar Drug Liking VAS

The 0-100 mm bipolar Drug Liking VAS is anchored by 0 = Strong Disliking, 50 = Neither Like nor Dislike, and 100 = Strong Liking. Subjects were required to respond to the statement “Do you like the drug effect you are feeling now?” Descriptive statistics and statistical analysis for Drug Liking VAS, as provided by the CDER Office of Biostatistics are provided in Tables 10 and 11.

Intranasal administration of the comparator, MS Contin 60 mg, resulted in a statistically significantly higher ($p < 0.0001$) mean Emax of Drug Liking compared to placebo (77.7 mm versus 54.7 mm) thereby validating each of these measures.

Intranasal EG001 high volume and intranasal EG001 low volume produced mean Emax scores of Drug Liking of 65.5 mm and 59.6 mm, respectively, that were statistically significantly lower ($p < 0.0001$) than the Emax of Drug Liking produced by intranasal MS Contin (77.7 mm). The median times to achieve Emax of Drug Liking were 1.01, 1.75, and 1.01 hours for intranasal MS Contin and intranasal high volume and low volume EG001, respectively.

Results – Unipolar High VAS

The 0-100 mm unipolar High VAS is anchored by 0 = Not at All and 100 = Extremely. Subjects were required to respond to the statement “I am feeling high.”

Intranasal administration of the comparator, MS Contin 60 mg, resulted in a statistically significantly higher ($p < 0.0001$) mean Emax of High compared to placebo (61.2 mm versus 10.7 mm) thereby validating this measure. (See Tables 10 and 11)

The mean Emax of intranasal MS Contin (61.2 mm) was statistically significantly ($p < 0.0001$) higher than that produced by either high volume (27.7 mm) or low volume (16.0 mm) intranasal EG-001. (See Tables 7 and 8). The times to achieve Emax of High were 2.00, 2.01, and 0.75 hours for the intranasal administration of MS Contin, high volume EG001, and low volume EG-001, respectively.

Results – Bipolar Take Drug Again VAS – 24 Hours

The 0-100 mm bipolar Take Drug Again VAS is anchored by 0 = Definitely Would Not, 50 = Do Not Care, and 100 = Definitely Would. Subjects were required to respond to the statement “Would you want to take the drug you just received again, if given the opportunity?”

Intranasal administration of the comparator, MS Contin 60 mg, resulted in a statistically significantly higher ($p < 0.0001$) mean Emax of Take Drug Again compared to placebo (69.9 mm versus 52.5 mm) thereby validating this measure. (See Tables 10 and 11)

Treatment with intranasal MS Contin resulted in a mean Take Drug Again Emax of 69.9 mm which was statistically significantly ($p < 0.0001$) higher than that observed following intranasal EG001 high or low volume (43.1 mm and 52.6 mm, respectively). (See Tables 10 and 11)

The overall results of the Take Drug Again VAS provided support for a deterrent effect of EG-001 tablets to abuse by insufflation.

Results – Bipolar Overall Drug Liking VAS – 24 Hours

The 0-100 mm bipolar Overall Drug Liking VAS is anchored by 0 = Strong Disliking, 50 = Neither Like nor Dislike, and by 100 = Strong Liking. Subjects were asked to respond to the statement “Overall, my liking for this drug is:”

Intranasal administration of the comparator, MS Contin 60 mg, resulted in a statistically significantly higher ($p < 0.0001$) mean Emax of Overall Drug Liking compared to placebo (72.7 mm versus 52.1 mm) thereby validating this measure. (See Tables 10 and 11)

With respect to Overall Drug Liking, the Emax produced by intranasal MS Contin (72.7 mm) was statistically significantly ($p < 0.0001$) higher than that produced by intranasal low volume and high volume EG001 (54.4 mm and 53.9 mm, respectively). (See Tables 7 and 8)

Results – Bipolar Ease of Snorting VAS

The 0-100 mm bipolar Ease of Snorting Assessment VAS is anchored by 0 = Very Difficult, 50 = Neither Easy nor Difficult, and by 100 = Very Easy. Subjects were asked to respond to the statement “Snorting the drug was:”

For the Ease of Snorting VAS, only the EG001 60 mg IN high volume treatment had low mean score that were within the “difficult” range of the scale (mean of 17.0 mm out of 100 mm). Mean scores for all other treatments were in the “easy” range of the scale and within 5 points of each other (range of mean scores 73.8 to 78.0).

Results – Subject Rated Nasal Effects Assessment

Nasal tolerability was examined using a Nasal Effects Assessment in which subjects were required to rate the degree of severity for “nasal irritation”, “nasal burning”, “runny nose/nasal discharge”, “facial pain/pressure”, “nasal congestion”, and “need to blow nose.” Rating these symptoms involved the use of a 4-point Likert scale with 0 = None, 1 = Mild, 2 = Moderate, and 3 = Severe.

For intranasal treatments including MS Contin 60 mg, EG-001 60 mg low volume, and placebo the mean maximum scores were ≤ 1 for all six nasal symptoms, indicating at most mild nasal effects following these treatments. Following intranasal 60 mg EG001 high volume mean maximum subjective nasal scores for “need to blow nose”, “nasal congestion”, “nasal irritation”, and “nasal congestion” were 2.1, 2.1, 1.5, and 1.3, respectively, indicating some mild-to-moderate nasal effects.

Overall, these results suggest that compared to the other treatments, including MS Contin manipulated, EG001 intranasal high volume was associated with some degree of nasal irritation. The extent to which this may have contributed to lower scores compared to MS Contin manipulated, for Drug Liking VAS, Take Drug Again VAS, or Overall Drug Liking VAS is not clear.

4.2 Adverse Event Profile Through all Phases of Development

As part of the Phase I clinical development program, Sponsor conducted the five clinical studies listed below.

- **Study 067-EG-001** entitled: “A Randomized, Open-Label, 6-Way Crossover Study to Determine the In Vitro/In Vivo Correlation of Various Formulations of Egalet Morphine 60 mg Prolonged-Release Dosage Units (Tests) and to Compare the Bioavailability Between These Formulations to Kadian (Reference 1), Avinza (Reference 2), and MS CONTIN (Reference 3) Following a 60 mg Dose Administered Under Fasting Conditions in Healthy Volunteers Using Naltrexone Blockade.”
- **Study 067-EG-002** entitled “A Randomized, Open-Label, 5-Way Crossover Comparative Bioavailability Study of Four Egalet PR Morphine Tablet 60 mg Formulations Versus MS Contin (60 mg) Administered Under Fasting Conditions to Healthy Subjects Using Naltrexone Blockade.”
- **Study 067-EG-006** entitled “A Randomized, Open-Label, 2-Way Crossover Study to Determine the Bioequivalence of the Egalet Morphine PR 15 mg Tablet Versus MS CONTIN Under Fasting Conditions in Healthy Subjects. 15 mg strength of morphine sulfate ER product was not bioequivalent to MS CONTIN 15 mg.”
- **Study 067-EG-011** entitled “A Randomized, Open-Label, 2-Cohort, Crossover Design Study to Determine the Bioequivalence of Egalet Morphine PR 60 mg Tablets Versus MS CONTIN 60 mg Tablets and to Evaluate the Effect of Food on Egalet Morphine PR 60 mg Tablets in Healthy Subjects with Naltrexone Blockade.”
- **Study 067-EG-012** entitled “A Randomized, Open-Label, 3-Way Crossover Study to Evaluate the Bioequivalence of Egalet Morphine PR 30 mg to MS Contin 30 mg and Egalet Morphine PR 2 x 15 mg to MS CONTIN 30 mg Under Fasting Conditions in Healthy Subjects under Naltrexone Blockage.”

Clinical studies 067-EG-001 and 067-EG-002 were pilot studies conducted on test formulations that were not the to-be-marketed formulation. The adverse events suggestive of abuse potential were not among the adverse events documented in these studies.

Pilot study 069-EG-006, as well as the two pivotal bioequivalence studies, 067-EG-011 and 067-EG-012 were conducted on “Formulation C”, the to-be-marketed product. This review will focus on the three studies using the to-be-marketed formulation (069-EG-006, 067-EG-011, and 067-EG-012). Two of these studies, namely 067-EG-011 and 067-EG-012, were conducted under naltrexone blockade.

A summary for treatment-emergent adverse events (TEAEs) reported from studies 069-EG-006, 067-EG-011, and 067-EG-012 is found in Table 12. Only in study 067-EG-006, conducted in the absence of naltrexone blockage, was there mention of abuse-related TEAEs. There was one case in which a subject reported “Euphoric Mood” following administration of 15 mg EG-001 that was considered mild and “probably” treatment related. Across the three studies and following treatments with EG-001 or MS Contin, the most common TEAEs were headache, nausea, vomiting, and dizziness.

Table 12. Summary of Treatment-Emergent Adverse Events (TEAEs) from Studies 069-EG-006, 067-EG-011, and 067-EG-012, Using the To-Be-Marketed Formulation).

Phase 1 Clinical Study	Total TEAEs (No. of Subjects)	Abuse Related TEAEs (MedDRA Version 16.1)	Other TEAEs Reported 2 or More Times (MedDRA Version 16.1)	
			Treatment	TEAEs (No. of Events)
067-EG-006	33 (19)	“Euphoric Mood” – 1 case - 15 mg EG-001 Fasted – mild, probably TXT related	EG-001 15 mg Fasted (n=64)	Headache (5), Dizziness (3), Nausea (3), Oropharyngeal pain (1), Cough (1), Contact Dermatitis (1)
			MS Contin 15 mg Fasted (n=64)	Headache (2), Dizziness (2), Nausea (2), Cough (1), Dermatitis Contact (1)
067-EG-011	48 (21)	NONE	EG-001 60 mg Fasted (n=64)	Nausea (9), Vomiting (6), Abdominal Pain (2), Diarrhoea (1), Headache (1), Dizziness (1), Somnolence (2), Cough (1)
			MS Contin 60 mg Fasted (n=62)	Nausea (5), Vomiting (1), Abdominal Pain (2), Diarrhoea (1), Headache (2), Somnolence (1), Cough (1)
			EG-001 60 mg Fed (n= 22)	Nausea (1), Vomiting (1), Headache (2), Dizziness (1)
067-EG-012	44 (20)	NONE	EG-001 30 mg Fasted (n=62)	Vomiting (2), Headache (1), Dizziness (1), Oropharyngeal pain (2), Dermatitis contact (1)
			MS Contin 30 mg Fasted (n=59)	Nausea (2), Headache (1), Dizziness (2), Oropharyngeal pain (1), Feeling Abnormal (1),
			2 x EG-001 15 mg Fasted (n- 62)	Nausea (3), Vomiting (2), Headache (5), Dizziness (1), Feeling Abnormal (1), Dermatitis contact (1)

4.3 Safety Profile

In the clinical program there were no deaths, accidental overdoses, overdoses associated with misuse/abuse, or unintended pediatric exposures

4.4 Evidence of Abuse, Misuse and Diversion in Clinical Trials

There were no reports of abuse, misuse, or diversion of EG-001 tablets or comparator drugs (MS Contin) during the Phase 1 clinical trials conducted in support of NDA 208603. No Phase 3 efficacy studies were conducted.

5. Regulatory Issues and Assessment

By virtue of containing morphine sulfate, EG-001 Tablets upon approval will be in Schedule II of the Federal Controlled Substances Act. Sponsor has not proposed any alternative scheduling action.

The statements below pertain to the Section 9 of the label as proposed by the Sponsor.

(b) (4)

- In vitro Category 1 extractability/syringeability studies indicate that EG-001 Tablets are difficult to manipulate for intravenous injection. At the same time, these studies demonstrate that the positive control, MS Contin, can easily be used to prepare suitable intravenous solutions. Based on these findings, a claim of deterrent effect to intravenous abuse for EG-001 is justified in Section 9.2 of the label.

(b) (4)

On August 4, 2016 an FDA Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety & Risk Management Advisory Committee was convened to examine the granting of abuse deterrent claims for EG-001 tablets. The joint committee voted to recommend giving EG-001 tablets abuse deterrent claims to oral, intranasal, and intravenous administration. The granting of an oral abuse deterrent claim was based primarily on the belief based on tablet hardness that EG-001 would provide resistance to abuse by chewing. There was no clear opinion expressed regarding to whether or not the results of oral study 067-EG-008 supported an oral abuse deterrent claim. CSS continues to maintain that study 067-EG-008 does not provide evidence of an oral abuse deterrent effect. This study did not involve manipulation of EG-001 by chewing, but instead by cutting into pieces using a chopping block and Chef's knife. In addition, at this time there is no evidence that EG-001 tablets may provide resistance to chewing.

6. Other Relevant Information

EG-001 Tablets have not previously been marketed in the United States or other countries. There is no mention of EG-001 Tablets in the scientific literature.

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/s/

JAMES M TOLLIVER
08/15/2016

MICHAEL KLEIN
08/15/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Drug Utilization Review**

Date:	June 30, 2016
Reviewer:	Joann H. Lee, Pharm.D. Drug Utilization Data Analyst Division of Epidemiology II (DEPI II)
Team Leader	Rajdeep Gill, Pharm.D. Drug Utilization Data Analysis Team Leader DEPI II
Deputy Director For Drug Utilization	LCDR Grace Chai, Pharm.D. DEPI II
Drug Name(s):	Arymo (morphine) Extended-Release (ER)
Application Type/Number:	NDA 208603
Applicant/sponsor:	Egalet, Inc.
OSE RCM #:	2016-950

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EXECUTIVE SUMMARY

In preparation for the upcoming joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) scheduled for August 4, 2016, this review summarizes the drug utilization analyses of morphine extended-release (ER) and other extended-release/long-acting (ER/LA) opioid analgesics to provide context and background information.

The Agency is currently considering approval of Arymo (morphine) ER (NDA 208603) with the indication of the management of pain severe enough to require daily, around the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The purpose of the Advisory Committee Meeting is to discuss whether the data submitted by the Sponsor for this new drug application of a single-entity morphine ER are sufficient to support product labeling that describe abuse-deterrent properties if the drug is approved.

This drug utilization review focused on the U.S. outpatient retail prescription utilization trends of morphine ER and all other ER/LA opioid analgesics from 2011 through 2015.

Our overall findings suggest that utilization of morphine ER remained relatively steady from 2011 through 2015 while utilization of oxycodone ER and methadone appeared to decline. Additionally, morphine ER was the top dispensed drug (6.4. million prescriptions dispensed) in the ER/LA opioid analgesic market with nearly one-third of morphine ER prescriptions written by family practice/general practice/osteopathy in 2015.

1 INTRODUCTION

This review summarizes the drug utilization patterns of morphine extended-release (ER) and other extended-release/long-acting (ER/LA) opioid analgesics to provide context and background information for the upcoming joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) scheduled for August 4, 2016. The purpose of this Advisory Committee Meeting is to discuss whether the data submitted by the Sponsor for a new drug application (NDA 208603) of a single entity morphine ER are sufficient to support product labeling with abuse-deterrent properties if the drug under consideration is approved.

1.1 BACKGROUND^{1,2,3}

Arymo (morphine) ER (NDA 208603) was submitted by the Sponsor with a proposed indication of the management of pain severe enough to require daily, around the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. This new drug is formulated with claims of abuse-deterrent properties.

Embeda (combination morphine ER/naltrexone), approved in 2009 and Morphabond (morphine ER), approved in 2015 are currently approved morphine containing ER opioid analgesics with labeling that describe abuse-deterrent properties. Embeda is included in the drug utilization data among the morphine containing products (see Table 1); however, drug utilization data for Morphabond was not available at the time of this review.

This drug utilization review is provided to support discussions on whether the data submitted by the Sponsor for a new drug application of morphine ER (NDA 208603) are sufficient for approval and for labeling with abuse-deterrent claims at the upcoming Advisory Committee Meeting scheduled for August 4, 2016.

1.2 PRODUCT INFORMATION

Table 1 provides the list of all brand and generic drug products covered under the ER/LA opioid analgesic REMS program included in this review:

¹ FR notice AADPAC.DSARM 08.04.16.docx Accessed June 2016 at: DAAAP Arymo shared folder \\fdafs01\ode2\DAAAP\NDA and sNDA\NDA 208603 (MS_Egalet)\AC.

² Open – BG 2 History of Abuse-Deterrent Opioids.docx Accessed June 2016 at: DAAAP Arymo shared folder \\fdafs01\ode2\DAAAP\NDA and sNDA\NDA 208603 (MS_Egalet)\AC.

³ Morphabond ER approval letter accessed June-2016 at: http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2016/206544Orig1s001ltr.pdf

Table 1. Morphine ER and all other opioid ER/LA opioid analgesic products⁴

Active Ingredient	Trade Name	Approval Date
Methadone tablets or liquid	Dolophine	March 14, 1973
Extended-release, Oral-dosage Forms Containing Active Ingredient		
Morphine ER	MS Contin	May 29, 1987
	Kadian	July 3, 1996
	Avinza	Feb 20, 2002
	Embeda (morphine/naltrexone)*	Aug 13, 2009
	Morphabond**	October 2, 2015
Oxycodone ER	OxyContin	December 12, 1995
	Targiniq (oxycodone/naloxone) [†]	July 23, 2014
Hydromorphone ER	Exalgo	March 1, 2010
Oxymorphone ER	Opana ER	June 22, 2006
Tapentadol ER	Nucynta ER	August 25, 2011
Hydrocodone ER	Zohydro ER	October 25, 2013
	Hysingla ER	November 20, 2014
Transdermal Delivery Systems		
Fentanyl Transdermal	Duragesic	August 7, 1990
Buprenorphine Transdermal	Butrans	June 30, 2010
*Embeda ER (morphine/naltrexone) was withdrawn from the market in March 2011 because of stability issues. It was approved with a manufacturing supplement in November 2013. **Morphabond approved in October 2015, drug utilization data not available for this review. [†]Targiniq ER (oxycodone/naloxone) is currently not marketed in the United States.		

⁴ Drugs at FDA: Approved Risk Evaluation and Mitigation Strategies (REMS) at <http://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemisDetails.page&REMS=17>. Accessed March-2016.

2 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct the analyses in this review (see Appendix B for full database descriptions).

2.1 DETERMINING SETTING OF CARE

The IMS Health, IMS National Sales Perspectives™ was used to determine various retail and non-retail channels of distribution for the ER/LA opioid analgesics. The sales data for 2015 show that approximately 86% of morphine ER bottles or packages were distributed to outpatient retail pharmacies (including chain, independent, and food stores). The sales data for all other ER/LA opioid analgesics (Table 1, Section 1.2) also show that majority of sales were towards retail pharmacies (including chain, independent, and food stores).⁵ Therefore, outpatient retail pharmacy utilization patterns were examined in this review for the opioid ER/LA analgesic products. Mail-order/specialty and non-retail settings were not included in this review.

2.2 DATA SOURCES USED

The IMS, National Prescription Audit™ (NPA) database was used to obtain nationally estimated number of prescriptions dispensed for morphine ER and all other ER/LA opioid analgesics (Table 1, Section 1.2) from U.S. outpatient retail pharmacies, from 2011 through 2015, annually.

The IMS NPA database was also used to obtain the nationally estimated number of prescriptions dispensed for morphine ER from U.S. outpatient retail pharmacies, stratified by top prescriber specialties for 2015.

3 RESULTS

3.1 PRESCRIPTION DATA

Figure 1 below and Table 2 in Appendix A show the nationally estimated number of ER/LA opioid analgesic prescriptions dispensed from U.S. outpatient retail pharmacies from 2011 through 2015.

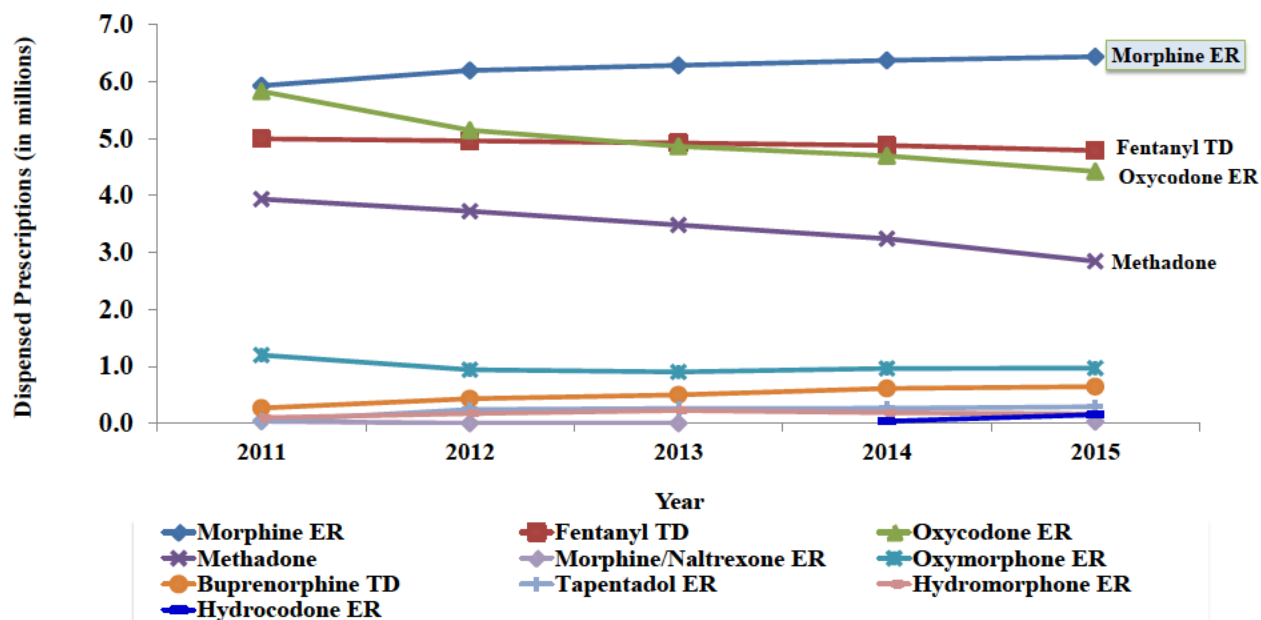
Approximately 21-22 million ER/LA opioid analgesic prescriptions were dispensed annually from 2011 through 2015. In 2015, morphine ER accounted for 31% (6.4 million prescriptions) of the total ER/LA prescriptions dispensed, followed by fentanyl transdermal (TD) (23%, 4.8 million prescriptions), and oxycodone ER (21%, 4.4 million prescriptions). Methadone prescriptions accounted for 14% (2.8 million prescriptions) of the total ER/LA prescriptions dispensed.

In terms of the yearly trends, dispensed prescriptions for morphine ER and fentanyl TD appeared to remain relatively stable from 2011 through 2015. Prescriptions for oxycodone ER and methadone decreased by approximately 24% and 28%, respectively, from 2011 through 2015.

⁵ IMS Health, IMS National Sales Perspective. Year 2015. Extracted March 2016. File: NSP 2016-950 channels morphine ERLA AC June 2016.xlsx

FIGURE 1

Nationally estimated number of prescriptions dispensed for ER/LA opioid analgesics from U.S. outpatient retail pharmacies from 2011 – 2015



Source: IMS, National Prescription Audits (NPA) Data extracted March 2016. File: NPA 2016-950 Rx morphine ERLA AC June 2016.xlsx
**No data for years 2011, 2012, and 2013 for hydrocodone products: Zohydro ER approved in 10/2013 and Hysingla ER approved 11/2014

3.2 PRESCRIBER SPECIALTY FOR MORPHINE ER

Table 3 in Appendix A provides the total number of prescriptions dispensed for morphine ER from U.S. outpatient retail pharmacies by the top prescribing specialties for year 2015. Family practice/general practice/osteopathy was the top prescriber specialty (27% of total prescriptions) followed by anesthesiology (13%), nurse practitioner (13%) and internal medicine (11%) in 2015.

4 DISCUSSION

This review provides drug utilization data for morphine extended-release (ER) and other extended-release/long-acting (ER/LA) opioid analgesics as background information in support of discussions for a new drug application (NDA 208603) of a single-entity morphine ER product. During the examined time period, the number of prescriptions dispensed for morphine ER appeared to remain relatively steady while utilization of oxycodone ER and methadone appeared to decline.

The prescription data showed that primary care providers such as family practice/general practice/osteopathy were the top prescriber specialties for morphine ER in 2015. Additionally, pain medicine specialists are likely the second top prescribers of morphine ER assuming anesthesiologists also overlap as pain specialists in the outpatient setting.

Findings from this review should be interpreted in the context of the known limitations of the databases used. Based on the IMS Health, IMS National Sales Perspectives™, sales data for 2015

showed that a vast majority of various ER/LA opioid bottles or packages were distributed to outpatient retail pharmacies. We focused our analysis on only the outpatient retail pharmacy settings; therefore, these estimates may not apply to other settings of care in which these products are used (e.g. mail-order setting, clinics, non-federal hospitals, etc.). The estimates provided are national estimates, but no statistical tests were performed to determine statistically significant changes over time or between products. All changes over time or between products should be considered approximate and may be due to random error.

5 CONCLUSION

Our overall findings suggest that utilization of morphine ER remained relatively steady from 2011 through 2015. Additionally, morphine ER was the top dispensed drug (6.4. million prescriptions dispensed), accounting for approximately 31% of the ER/LA opioid analgesic market. Nearly one-third of morphine ER prescriptions dispensed were written by family practice/general practice/osteopathy in 2015.

6 APPENDICES

6.1 APPENDIX A: TABLES

TABLE 2.

Nationally estimated number of prescriptions dispensed for ER/LA opioid analgesics from U.S. outpatient retail pharmacies, 2011-2015

	2011		2012		2013		2014		2015	
	Prescriptions (N)	Share (%)	Prescriptions (N)	Share (%)	Prescriptions (N)	Share (%)	Prescriptions (N)	Share (%)	Prescriptions (N)	Share (%)
Grand Total	22,330,862	100.0%	21,817,818	100.0%	21,446,002	100.0%	21,256,647	100.0%	20,742,630	100.0%
Morphine ER	5,931,628	26.6%	6,198,303	28.4%	6,288,088	29.3%	6,375,570	30.0%	6,441,121	31.1%
Fentanyl TD	4,997,384	22.4%	4,961,133	22.7%	4,923,139	23.0%	4,881,447	23.0%	4,791,686	23.1%
Oxycodone ER	5,831,523	26.1%	5,148,631	23.6%	4,865,489	22.7%	4,699,154	22.1%	4,423,455	21.3%
Methadone	3,938,607	17.6%	3,725,332	17.1%	3,484,537	16.2%	3,242,281	15.3%	2,846,882	13.7%
Oxymorphone ER	1,196,953	5.4%	939,908	4.3%	901,305	4.2%	960,933	4.5%	968,029	4.7%
Buprenorphine TD	266,332	1.2%	431,793	2.0%	497,697	2.3%	613,086	2.9%	643,634	3.1%
Tapentadol ER	37,531	0.2%	242,059	1.1%	259,294	1.2%	264,048	1.2%	289,459	1.4%
Hydromorphone ER	95,823	0.4%	170,654	0.8%	226,452	1.1%	185,035	0.9%	160,632	0.8%
Hydrocodone ER	—	—	—	—	—	—	35,093	0.2%	149,957	0.7%
Morphine/Naltrexone ER	35,081	<1%	5	<0.1%	1	<0.1%	—	—	27,775	<1%

Source: IMS, National Prescription Audit (NPA). Extracted April 2016. File: NPA 2016-950 Rx morphine ERLA AC June-2016.xlsx

TABLE 3.

Nationally estimated number of prescriptions dispensed for morphine ER from U.S. outpatient retail outpatient pharmacies, stratified by top 10 prescriber specialties, for year 2015

PRESCRIBER SPECIALTY	Prescriptions (N)	Share (%)
Morphine ER Total Prescriptions	6,441,121	100.0%
Family Practice/General Practice/Osteopathy	1,706,226	26.5%
Anesthesiology	863,681	13.4%
Nurse Practitioner	811,374	12.6%
Internal Medicine	709,509	11.0%
Physician Assistant	619,726	9.6%
Physical Medicine/Rehabilitation	524,352	8.1%
Pain Medicine	362,184	5.6%
Oncology	217,555	3.4%
Neurology	96,472	1.5%
Orthopedic Surgery	67,299	1.0%
All Other Specialties	462,743	7.2%

Source: IMS, National Prescription Audit (NPA). Year 2015. Extracted June-2016. File: NPA 2016-950 specialty morphine ERLA AC June 2016.xlsx

6.2 APPENDIX B: DRUG USE DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS, National Prescription Audit

The National Prescription Audit (NPATM) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPATM receives over 2.7 billion prescription claims per year, captured from a sample of the universe of approximately 57,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 86% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 40 - 70% (varies by class and geography) of mail service pharmacies and approximately 45-55% of long-term care pharmacies. Data are available on-line for 72- rolling months with a lag of 1 month.

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/s/

JOANN H LEE
08/08/2016

RAJDEEP K GILL
08/08/2016

JUDY A STAFFA
08/08/2016

MEMORANDUM

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

DATE: July 11, 2016

TO: Sharon Hertz, M.D.
Director
Division of Anesthesia, Analgesia, and Addiction
Products (DAAAP)
Office of Drug Evaluation II
Office of New Drugs

FROM: Xingfang Li, MD, RAC
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Inspection of PPD Phase I Clinic, Austin, TX
covering the following application:

NDA 208603 [Morphine Sulfate Extended Release Tablet,
sponsored by Egalet US Inc., USA]

Reviewer's Recommendation: This OSIS reviewer recommends that the results from clinical portions of the following studies should be accepted for further Agency review.

The inspection was conducted by ORA Investigator Maira Brading at PPD Phase I Clinic, Austin, TX, from May 23 to June 3, 2016. The inspection was initiated in support of review of **NDA 208603**. The clinical portions of the following studies were audited:

Study #: 067-EG-011

Study Title: "A Randomized, Open-Label, 2-Cohort, Crossover Design Study To Determine The Bioequivalence Of Egalet Morphine PR 60 mg Tablets Versus MS Contin® 60 mg Tablets And To Evaluate The Effect Of Food On Egalet Morphine PR 60 mg Tablets In Healthy Subjects With Naltrexone Blockade"

Study Period: 3/16/2015-5/13/2015

Study #: 067-EG-012

Study Title: "A Randomized, Open-Label, 3-Way Crossover Study To Evaluate The Bioequivalence Of Egalet Morphine PR 30 mg To MS Contin 30 mg And Egalet Morphine PR 2 x 15 Mg To MS Contin® 30 Mg Under Fasting Conditions In Healthy Subjects Under Naltrexone Blockade"

Study Period: 11/12/2014-01/27/2015

The audit included a thorough review of study records, including study protocol compliance, informed consent, institutional review board approvals, and case report forms, and examination of facilities and test article accountability, as well as interviews and discussions with the firm's management and staff.

Following the inspection, no objectionable conditions were found and no Form FDA-483 was issued.

Conclusions:

Following a review of the inspection report, this reviewer recommends that results from clinical portions of studies 067-EG-011 and 067-EG-012 should be accepted for further Agency review.

Final Classification:

NAI: PPD Phase I Clinic, Austin, TX
(FEI: 3008374644)

Xingfang Li, MD, RAC
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

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ORA/Brading Maira

Draft: XFL 7/11/2016
Edits: MFS 7/11/2016; JC 7/15/2016
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/ PPD Phase I Clinic, Austin, TX
OSIS file #BE7114; NDA 208603

FACTS: 11620631

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/s/

XINGFANG LI
07/15/2016

MICHAEL F SKELLY
07/15/2016

SEONGEUN CHO
07/15/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: March 30, 2016
Requesting Office or Division: Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
Application Type and Number: NDA 208603
Product Name and Strength: Arymo ER (morphine sulfate) Extended-release Tablets
15 mg, 30 mg, 60 mg
Submission Date: March 22, 2016
Applicant/Sponsor Name: Egalet US, Inc.
OSE RCM #: 2015-2715-1
DMEPA Primary Reviewer: James Schlick, RPh, MBA
DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

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

2 CONCLUSION

The revised container labels for Arymo ER are acceptable from a medication error perspective. We have no further recommendations at this time.

¹ Schlick J. Label and Labeling Review for Arymo ER (NDA 208603). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 MAR 11. 7 p. OSE RCM No.: 2015-2715.

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/s/

JAMES H SCHLICK

03/30/2016

BRENDA V BORDERS-HEMPHILL

03/30/2016

LABEL AND LABELING REVIEW

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

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

Date of This Review:	March 11, 2016
Requesting Office or Division:	Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 208603
Product Name and Strength:	Arymo ER (morphine sulfate) Extended-release Tablets 15 mg, 30 mg, 60 mg
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Egalet US, Inc.
Submission Date:	December 14, 2015
OSE RCM #:	2015-2715
DMEPA Primary Reviewer:	James Schlick, RPh, MBA
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

As part of the approval process for Arymo ER, DAAAP requested that we review the proposed label and labeling for areas that may lead to medication errors. Arymo ER is an opioid product with abuse deterrent properties, and Egalet uses MS Contin as their reference listed drug (RLD) in their 505(b)(2) NDA application.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	N/A B
Human Factors Study	N/A C
ISMP Newsletters	N/A D
FDA Adverse Event Reporting System (FAERS)*	N/A E
Other	N/A F
Labels and Labeling	G

N/A=not applicable for this review

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Egalet proposes to introduce an extended release morphine sulfate tablet containing three strengths (15 mg, 30 mg, and 60 mg). (b) (4)

If a patient requires a high dose of morphine (i.e. 180 mg), we do not believe that taking three 60 mg tablets of Arymo ER to make a 180 mg dose will create an excessive tablet burden for the patient. Thus, we find the proposed strengths acceptable.

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

Container Labels

After our review of the container labels, we recommend that (b) (4) Arymo ER, on the principal display panel be removed or significantly reduced to prevent potential confusion. We are concerned (b) (4) could distract health care practitioners from the modifier 'ER' and dosage form "extended-release tablets". Postmarketing reports

have shown selection errors between immediate-release and extended-release oral tablet morphine products.

We also identified other areas of the container labels that can be improved to mitigate the risk of confusion that can lead to medication error. These areas are listed as follows:

- The font size of the CII symbol is too large and distracts from the proprietary name, established name, and strength which should be the most prominent information on the label.
- The strength statement should be centered below the proprietary and established names and the font size increased. This makes it more likely that the strength will be read correctly due to the curvature of the bottle.¹

Prescribing Information

We reviewed the prescribing information and determined that it is acceptable from a medication error perspective. We have no recommendations at this time.

4 CONCLUSION & RECOMMENDATIONS

We recommend that Egalet decrease or remove certain information on the principal display panel to increase the readability and prominence of the proprietary name, established name, and the dosage form on the proposed container labels to promote the safe use of the product. We also provide a recommendation to improve the readability of the strength. These recommendations to Egalet can be found in Section 4.1 to address these concerns.

¹ Institute for Safe Medication Practices. Safety briefs: Label Characteristic contributes to errors. ISMP Med Safety Alert Community/Ambulatory Care. 2016;15(1):1-8.

4.1 RECOMMENDATIONS FOR EGALET

We recommend the following be implemented prior to approval of this NDA:

A. Container Label

1. We recommend that (b) (4), Arymo ER, on the principal display panel be removed or significantly reduced to prevent potential confusion. We are concerned (b) (4) could distract health care practitioners from more important information such as the modifier 'ER' and dosage form "extended-release tablets". Postmarketing reports have shown selection errors between immediate-release and extended-release oral tablet morphine products. Additionally (b) (4) and can result in misinterpretation of the proprietary name.
2. Decrease the font size of the CII symbol to ensure that the proprietary name, established name, and strength are the most prominent information on the label.
3. The strength statement (i.e. 15 mg, 30 mg, and 60 mg) should be centered below the proprietary and established names and the font size increased. This makes it more likely that the strength will be read correctly due to the curvature of the bottle.¹

¹ Institute for Safe Medication Practices. Safety briefs:. Label Characteristic contributes to errors. ISMP Med Safety Alert Community/Ambulatory Care. 2016;15(1):1-8.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

Table 2 presents relevant product information for Arymo ER that Egalet US, Inc. submitted on December 14, 2015, and the listed drug (LD).

Table 2. Relevant Product Information for Arymo ER and the Listed Drug		
Product Name	Arymo ER	MS Contin
Initial Approval Date	N/A	May 29, 1987
Active Ingredient	Morphine sulfate	Morphine sulfate
Indication	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment.	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment.
Route of Administration	Oral	Oral
Dosage Form	Extended-release tablets	Extended-release tablets
Strength	15 mg, 30 mg, 60 mg	15 mg, 30 mg, 60 mg, 100 mg, 200 mg
Dose and Frequency	15 mg to 120 mg orally every 8 to 12 hours	15 mg to 100 mg orally every 8 to 12 hours
How Supplied	Bottles containing 100 tablets	Bottles containing 100 or 500 tablets
Storage	Room temperature	Room temperature

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,³ along with postmarket medication error data, we reviewed the following Arymo ER labels and labeling submitted by Egalet US, Inc. on December 14, 2015.

- Container label
- Carton labeling
- Prescribing Information – No image

G.2 Label and Labeling Images



³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JAMES H SCHLICK

03/11/2016

BRENDA V BORDERS-HEMPHILL

03/14/2016

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

PATIENT LABELING REVIEW

Date: October 11, 2016

To: Sharon Hertz, MD
Director
**Division of Anesthesia, Analgesia, and Addiction Products
(D AAAP)**

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

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

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

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

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name),
Dosage Form and
Route: ARYMO ER (morphine sulfate) extended-release tablets, for
oral use, CII

Application
Type/Number: NDA 208603

Applicant: Egalet

1 INTRODUCTION

On December 14, 2015, Egalet submitted for the Agency's review a New Drug Application (NDA) 208603 for ARYMO ER (morphine sulfate) extended-release tablets, an abuse-deterrent opioid. ARYMO ER (morphine sulfate) extended-release tablets are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAA P) on July 26, 2016, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ARYMO ER (morphine sulfate) extended-release tablets.

2 MATERIAL REVIEWED

- Draft ARYMO ER (morphine sulfate) extended-release tablets MG received on December 14, 2015, and received by DMPP and OPDP on September 30, 2016.
- Draft ARYMO ER (morphine sulfate) extended-release tablets Prescribing Information (PI) received on December 14, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 30, 2016.

3 REVIEW METHODS

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

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

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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immediately following this page

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/s/

MORGAN A WALKER
10/11/2016

SAMUEL M SKARIAH
10/11/2016
Signing for Koung Lee

BARBARA A FULLER
10/11/2016

LASHAWN M GRIFFITHS
10/11/2016

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

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

Memorandum

Date: October 7, 2016

To: Christopher Hilfiger, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Sharon Hertz, MD, Director - DAAAP

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

Through: Samuel Skariah, Team Leader - OPDP

CC: Olga Salis, Senior Regulatory Project Manager - OPDP

Subject: NDA 208603
Arymo ER (morphine sulfate) Extended-release Tablets
Professional Labeling Review

As requested in DAAAP's consult dated February 3, 2016, OPDP has reviewed the substantially complete prescribing information and container labels for Arymo ER Tablets. The substantially complete prescribing information was provided to OPDP on October 7, 2016, via email by Christopher Hilfiger with the file name "[\\fdsfs01\ode2\DAAAP\NDA and sNDA\NDA 208603 \(MS Egalet\)\Labeling\Arymo Label to consultants PLLR 10-6-16.docx](#)".

OPDP has provided comments on the substantially complete prescribing information in the attached document below. Specifically, we have comments on pages 22 and 24.

OPDP has no comments on the container labels submitted on March 22, 2016.

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

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/s/

KOUNG U LEE
10/07/2016

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

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

Application: NDA 208603

Application Type: New NDA

Drug Name(s)/Dosage Form(s): Arymo (morphine sulfate) 15 mg, 30 mg, 60 mg extended-release tablets

Applicant: Egalet US Inc.

Receipt Date: December 14, 2015

Goal Date: October 14, 2016

1. Regulatory History and Applicant's Main Proposals

NEW NDA

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

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

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- NO** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. **Instructions to complete this item:** If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment: *Waived in the referenced drug*

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Headings in HL must be presented in the following order:

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

Selected Requirements of Prescribing Information

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

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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

Comment:

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

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

Comment:

Boxed Warning (BW) in Highlights

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

Comment:

- YES** 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the

Selected Requirements of Prescribing Information

BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

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

Comment:

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

Comment:

Recent Major Changes (RMC) in Highlights

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

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

Adverse Reactions in Highlights

Selected Requirements of Prescribing Information

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “To report **SUSPECTED ADVERSE REACTIONS**, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.”

Comment:

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

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

- See 17 for **PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

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

Comment:

Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015** ”).

Comment:

Contents: Table of Contents (TOC)

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

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS.”** This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- YES** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading **“FULL PRESCRIBING INFORMATION: CONTENTS*”** must be followed by an asterisk and the following statement must appear at the end of the TOC: **“*Sections or subsections omitted from the full prescribing information are not listed.”**
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "[see *Warnings and Precautions (5.2)*]."

Comment:

Selected Requirements of Prescribing Information

- N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- YES 35. All text in the BW should be **bolded**.

Comment:

- YES 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

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

Comment:

- N/A 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

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

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
 - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

- YES** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

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

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

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

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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