CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208603Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	Division Director Summary Review
NDA #	208603
Applicant Name	Egalet US, Inc.
Date of Submission	December 14, 2015
PDUFA Goal Date	October 14, 2016
Proprietary Name / Established (USAN) Name	ARYMO ER (morphine sulfate extended-release tablets)
Dosage Forms / Strength	Tablet/15 mg, 30 mg, and 60 mg
Proposed 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.
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	John Hariadi, MD; John Feeney, MD
Pharmacology Toxicology Review	Grace S Lee, PhD; Elizabeth Bolan, PhD; R. Daniel Mellon, PhD
CMC and Biopharmaceutics Reviews	Debasis Ghosh, PhD; Donna Christner, PhD; Haitao Li, PhD; Pei-I Chu, PhD; Frank Wackes, PhD; Derek Smith, PhD; Christopher Hough, PhD; Venkateswara R. Pavuluri, PhD, RPh; An-chi (Angela) Lu, PharmD, Haritha Mandula, PhD; Steven Kinsley, PhD Ciby J. Abraham, PhD; Julia C. Pinto, PhD
Clinical Pharmacology Review	Srikanth Nallani, PhD; Yun Xu, PhD
CDTL Review	John Feeney, MD
OSE/DMEPA	James Schlick, RPh, MBA; Vicky Borders-Hemphill, PharmD
OPDP/DCDP	Koung Lee; Samuel Skariah
OMP/DMPP	Morgan Walker, PharmD, MBA, CPH; Barbara Fuller, RN, MSN, CWOCN
Controlled Substance Staff	James M Tolliver, PhD; Michael Klein, PhD
Abuse Potential Statistical Review	Wei Liu, PhD; Qianyu Dang, PhD; Yi Tsong, PhD
DPMH	Miriam Dinatale, DO; Lynne Yao, MD

OND=Office of New Drugs
DMEPA=Division of Medication Errors Prevention
CDTL=Cross-Discipline Team Leader
DCDP=Division of Consumer Drug Promotion
DMPP=Division of Medical Policy Programs
OSE= Office of Surveillance and Epidemiology
DSI=Division of Scientific Investigations
OPDP=Office of Prescription Drug Promotion
OMP=Office of Medical Policy Initiatives

Signatory Authority Review Template

1. Introduction

The Applicant has submitted a 505(b)(2) NDA for Arymo (morphine sulfate) Extended-Release Tablets relying in part on the Agency's previous findings of efficacy and safety for NDA 019516, MS Contin (morphine sulfate extended-release tablets) as a listed drug and on published literature. Arymo ER was developed with the proposed indication for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate and with properties intended to deter abuse by the oral, nasal, and intravenous routes of administration. This memo will focus on the evaluation of the abuse-deterrent properties of Arymo ER.

2. Background

Arymo ER was developed under IND 117317 and the development program was designated as Fast Track on February 18, 2014. The Applicant has provided a complete assessment of the chemistry, manufacturing, and controls data, clinical pharmacology studies to evaluate the pharmacokinetic profile of the product and bioequivalence to MS Contin, and in vitro and in vivo studies to evaluate the abuse-deterrent properties of the formulation. In lieu of conducting nonclinical studies and clinical studies of the safety and efficacy for the proposed indication, the Applicant is relying on the Agency's previous findings of efficacy and safety for MS Contin.

The Arymo ER tablet consists of a matrix containing the active drug substance, morphine sulfate, along with polyethylene oxide (PEO) and butylated hydroxytoluene, and a film coating. The extended-release profile and abuse-deterrent characteristics are based on excipients and a production method that uses an injection molding technique. The proposed tablet strengths for marketing are 15 mg, 30 mg and 60 mg. (b) (4)

In general, the primary route of abuse of opioid analgesics is oral, followed by different frequencies of intranasal and intravenous abuse depending on the specific product. This is true for both immediate-release and extended-release products. When extended-release products are manipulated to defeat the extended-release characteristics resulting in an earlier peak drug level, the risk for overdose increases. The approach to making Arymo ER abuse-deterrent relies on physicochemical properties to make defeat of the extended-release characteristics more difficult. It is important to remember that even when a product has abuse-deterrent properties that may reduce abuse through manipulation, it does not mean that there is no risk of abuse or addiction. It means, rather, that the risk of abuse is lower than it would be without such properties.

Arymo ER will be the second single-entity extended-release morphine product with abuse-deterrent (AD) properties on the US market. Morphabond (NDA 206544) was the first, approved on October 2, 2015, with labeling that describes in vitro data supporting that Morphabond has physiochemical properties expected to make abuse via injection difficult, and clinical data from a human abuse potential study and in vitro data that support the conclusion that Morphabond has physicochemical properties that are expected to reduce abuse by the intranasal route of administration. Morphabond qualified for 3-year exclusivity, which will expire on October 2, 2018, 3 years after the date of approval. This exclusivity is currently reflected in the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), with Exclusivity Code M-189, described as "labeling describing the expected reduction of abuse of single-entity extended-release morphine by the intranasal route of administration due to physicochemical properties".

As described below and during the August 4, 2016, joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee, a clinical abuse potential study demonstrated that Arymo ER has properties that can be expected to reduce abuse by the intranasal route. However, because the scope of Morphabond's exclusivity is for labeling describing the expected reduction of abuse of single-entity extended-release morphine by the intranasal route of administration due to physicochemical properties, a 505(b)(2) application (or ANDA) for a single-entity extended-release morphine product generally could not be approved for this same condition of approval until the expiration of Morphabond's 3-year exclusivity, i.e., until October 2, 2018. Thus, the Applicant has sought approval for Arymo ER without this exclusivity-protected condition of approval, and the drug will not be approved with this exclusivity-protected condition of approval. The Agency determined, however, that Arymo ER (1) could be approved with labeling stating that in vitro data demonstrate that Arymo ER has physiochemical properties that make abuse by injection difficult, and (2) otherwise meets the requirements for approval.

More information about Arymo ER is available in the briefing materials[1] from the August 4, 2016 Advisory Committee meeting. As described in the Guidance for Industry, Abuse-Deterrent Opioids – Evaluation and Labeling,[2] the development of abuse-deterrent formulations of opioid analgesics is recognized by FDA as an important approach to reducing abuse of prescription opioids. Prescription opioid products are an important component of modern pain management. However, abuse and misuse of these products have created a serious and growing public health problem. One potentially important step towards the goal of creating safer opioid analgesics has been the development of opioids that are formulated to deter abuse. FDA considers the development of these products a high public health priority.

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[1] http://www fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm514372 htm

[2] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf

3. CMC/Biopharmaceutics

The following Summary of Quality Assessments has been excerpted verbatim from the combined CMC review:

Product Overview

The applicant has developed an extended-release, oral morphine formulation 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. ARYMO ER was designed using Egalet's Guardian™ Technology, which utilizes a polymer matrix tablet technology involving an injection molding process. The tablets possess controlled- release properties as well as physical and chemical features that may resist some common methods of manipulation. Guardian™ Technology is designed to make the tablets harder than typical tablets (>400 N) which in theory would make it more resistant to particle size reduction and therefore more challenging to extract morphine sulfate. In addition, the technology results in a viscous hydrogel on contact with aqueous media, making syringeability more challenging. The majority of the physical manipulation attempts on ARYMO ER tablets resulted in particle sizes > 500 microns. Among the manually operated tools, the knife appears to be the most efficient tool in terms of producing particles less than 1,000 µm, which was not possible with the spoon, mortar and pestle, pill crusher, and hammer. Household electrical tools such as spice grinder and coffee grinder appear to be moderately effective for particle size reduction, when operated intermittently to prevent overheating and damage of the equipment components. The gelling nature of the formulation in aqueous media appears to restrict morphine extraction even when significant effort was expended for particle size reduction. Additional information can be found about the in vitro evaluation of category 1 studies in the CMC review.

Swelling in vitro experiments were conducted on the 15 mg and 60 mg tablets. The tablets were submerged in 1600 mL of liquid media where they were fully submerged. When the tablets were submerged for 30 seconds, they swelled to approximately 105% of the tablets weight in the liquid media. During the first three minutes, the outer coating of the tablet started to dissolve and swelled to 114-117%. Between 3.75-4.75 hours, the range of the swelling was observed to be 249-274%.

Morphine sulfate is a white to off-white crystalline solid that is very soluble in hot water, soluble in glycerin, sparingly soluble in anhydrous ethanol. The aqueous solubility of morphine sulfate depends on pH, but is mostly ionized at physiological pH with highest solubility at around pH 5.6- 5.7 and decreases gradually as pH of the media increases to 8.0. (b) (4) Morphine sulfate is non-hygroscopic. Morphine sulfate has a retest period of (b) (4) months. A letter of authorization was provided by the applicant to access DMF# (b) (4) The DMF is adequate for this application.

ARYMO ER are oral tablets that consist of a matrix containing the active substance, morphine sulfate, along with Polyethylene Oxide 400,000 ((b) (4)) and butylated hydroxytoluene.
ARYMO ER tablets are available in three strengths: 15 mg, 30 mg and 60 mg. Each strength is coated with a color to differentiate between the strengths:

ARYMO ER tablets, 15 mg are blue film coated, capsule shaped tablets debossed with EGLT 15.
ARYMO ER tablets, 30 mg are light purple film coated, capsule shaped tablets debossed with EGLT 30.
ARYMO ER tablets, 60 mg are light orange film coated, capsule shaped tablets debossed with EGLT 60.

Based on the stability data provided, an expiry of 24-months will be granted using the storage statement Store at 25°C (77°F); excursions permitted between 15° and 30°C (59° and 86°F). [See USP Controlled Room Temperature]. All strengths of ARYMO ER tablets are packaged in 200 cc high-density polyethylene (HDPE) bottles (b) (4) . Each bottle contains two oxygen absorber canisters and has a (b) (4) closure with (b) (4) seal.

The following has been excerpted verbatim from the CMC review of the in vitro assessment of abuse-deterrent properties:

(b) (4)

Following is the summary evaluation of various category 1 laboratory based in vitro manipulations and extraction studies conducted with the to-be-marketed-product of ARYMO ER (EG-001), challenging the physical and chemical features (e.g. hardness, gelling features, burning, extraction and extended-release properties) (b) (4)

1. ARYMO™ ER (EG-001) appears to resist the most common methods of physical manipulations. The planned physical manipulation performed using tablets with and without pre-treatment, i.e. heating and freezing conditions, doesn't appear to change the outcome of the manipulations. Serial physical manipulations performed using multiple modes of size reduction, as suggested by the FDA during type A meeting, doesn't appear to significantly change the particle size distribution.

2. ARYMO™ ER appears to possess physical and chemical features that resist extraction in to small volumes (up to 10 mL) of media, from intact and pre-treated tablets. The physically manipulated tablets also appear to retain gelling properties and resist extractions in small volumes. Combined with the Syringeability and injectability studies performed using water and hypertonic saline, the small volume

extraction studies on EG-001 appear to possess abuse-deterrent features that make abuse via injection route difficult.

3. The cumulative percent of morphine extracted from cut and ground tablets in a large volume (200 mL) of commonly available liquids and alcoholic solvents is significantly higher in the first two hours compared to intact tablets. The cumulative percent of morphine released from intact tablets after the first two hours period has decreased with increasing concentration of alcohol in the dissolution media.
4. Simulated smoking tests, to evaluate the likelihood of success of attempts to directly smoke (vaporize) drug from the formulation, appears to be unsuccessful releasing a very low percent of active when compared with the base and salt forms used as comparators.
5. Precipitation and isolation of morphine free base appears to be possible, using complex multi-step physical and chemical manipulations followed by extraction in to low boiling non-ingestible solvents and subsequent evaporation of solvent.

Dr. Pavuluri noted the following:

> Apart from initial evaluation of abuse-deterrent features (ADFs) of an opioid drug product during development, it is critical to assure that marketed ARYMO™ ER tablets maintain the ADFs as labeled through the end of shelf-life and during the life-cycle management. For this purpose, we propose the following PMR/PMC.

(b) (4)

[redacted] (b) (4)

The Dr. Lu found the dissolution method and specifications acceptable. Upon review of the proposed In Vitro In Vivo Correlation (IVIVC), Dr. Lu found that the Applicant did not conduct the model development according to the agency's recommended methods, so she evaluated additional approaches to attempt to validate the IVIVC model. Her analyses found that the IVIVC model from the Applicant [redacted] (b) (4), and hence, is inadequate.

Dr. Lu reviewed the in vitro alcohol interaction study and concurred with the finding that exposure to 5%, 10%, 20% and 40% alcohol solutions resulted in a progressively slower release rate of morphine from Arymo ER compared to morphine release from Arymo ER in the absence of alcohol.

I concur with the conclusions reached by the chemistry review team regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. I concur with the findings of the in vitro evaluation of the abuse-deterrent properties of Arymo ER and with the proposed PMR. Stability testing supports an expiry of 24 months. There are no outstanding issues that preclude approval.

4. Nonclinical Pharmacology/Toxicology

As noted by Dr. Lee:

> No new pharmacology, general toxicology, genetic toxicology, reproductive and developmental toxicology, or carcinogenicity studies were conducted or required for this application. The Applicant has submitted studies to qualify [redacted] (b) (4) a drug product degradant, which exceeds the ICH Q3B(R2) threshold for qualification. Justification has also been provided for several excipients, including polyethylene oxide [redacted] (b) (4) (PEO; MW: 400,000), [redacted] (b) (4) when the product is consumed at the maximum theoretical daily dose of morphine.
>
> All impurities in the drug substance and degradants in the drug product are controlled at acceptable levels. The proposed drug product degradant specification for [redacted] (b) (4) [redacted] (b) (4) which exceeds the ICH the Q3B(R2) threshold for qualification, has been justified and is considered acceptable. For qualification, the Applicant submitted an Ames assay, an in vitro chromosome aberration (CA) assay, and a 13-week repeat-dose rat toxicology study with [redacted] (b) (4). [redacted] (b) (4) was negative for genotoxic potential in both the Ames and CA assays. The NOAEL in the 13-week rat study was the highest dose tested, but did not support the specification of [redacted] (b) (4) % proposed by the Applicant. However, this application references MS Contin and the proposed specification is within the specification for [redacted] (b) (4) in MS Contin. Therefore, the proposed specification for [redacted] (b) (4) of [redacted] (b) (4) % will be considered acceptable for this NDA.

Arymo ER contains excipients that are intended to confer abuse-deterrent properties. (b) (4). With the exception of the PEO, the levels of the excipients in this product are considered acceptable and do not require qualification. (b) (4) To support the safety of the levels of the PEO in this product, the Applicant is referencing MF (b) (4) Master File (b) (4) has been found to be inadequate (b) (4) These (b) (4) entities could include (b) (4) and specifications for these impurities in the excipient master file may be required. However, because of the longstanding history of use of PEO in many products which reference MF (b) (4), this deficiency will not be an approval issue for NDA 208603. The levels of PEO in Arymo ER when used at the MTDD of MS are considered acceptable from a pharmacology/ toxicology perspective for this NDA. Pharmacology toxicology recommends that the Applicant conduct several studies as post-marketing requirements (PMR) to fully characterize the toxicity of the PEO. The recommended studies are outlined in Section 1.3.2.

The Applicant has submitted a literature review and proposed labeling changes for Section 8 (Pregnancy) in order to comply with the Pregnancy and Lactation Labeling Rule (PLLR). No new reproductive toxicology studies were submitted. In addition, a thorough review of the morphine literature was conducted by Dr. Grace Lee and is attached as an appendix to this review. The language for Section 8 of the label will be updated with this information.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. I also concur with the postmarketing requirements suggested to address the deficiencies from the review of DMF (b) (4), reproduced at the end of this memo.

5. Clinical Pharmacology

The Applicant conducted three studies to establish bioequivalence of Arymo ER to MS Contin for the 15 mg, 30 mg, and 60 mg strengths. (b) (4)

In Study 067-EG-011, the Applicant demonstrated bioequivalence of the to-be-marketed formulation of Arymo ER to MS Contin with the 60 mg strength tablet, as shown in the following table from Dr. Nallani's review, (page 6).

Table : Bioequivalence Analysis of AUC_t, AUC_∞, and C_{max} Parameters of Morphine (Pharmacokinetic Analysis Population), Study 067-EG-011

Pharmacokinetic Parameter (units)	n		Geometric LS Means		Geometric LS Mean Ratio (%) (Test:Reference) (90% CI)
	Test	Reference	Test	Reference	
AUC_∞ (ng•h/mL)	59	59	188.0	192.2	97.79 (95.07, 100.59)
AUC_t (ng•h/mL)	60	60	180.3	185.3	97.32 (94.27, 100.47)
C_{max} (ng/mL)	60	60	20.22	21.20	95.35 (89.40, 101.69)

As demonstrated in the following table also from page 6 of Dr. Nallani's review, there was a difference in median Tmax. Arymo ER is intended to be dosed on an around-the-clock basis. So in contrast to an analgesic that may be dosed on an as needed basis, the delay in Tmax for Arymo ER relative to MS Contin is not expected to have any clinical consequence.

Table: Descriptive Statistics of morphine PK in Study 067-EG-011

	Morphine	
	EG-001 60 mg Tablet Fasting Conditions Treatment A (n=60)	MS Contin 60 mg Tablet Fasting Conditions Treatment B (n=60)
AUC_∞ (ng•h/mL)	196.6 (27.3)	200.5 (26.8)
AUC_t (ng•h/mL)	189.1 (27.3)	192.8 (26.3)
C_{max} (ng/mL)	21.6 (35.6)	22.7 (36.5)
t_{max} (h)	4.50 (1.00, 6.00)	2.50 (0.67, 4.52)
$t_{½}$ (h)	9.57 (26.3)	9.94 (28.5)

Bioequivalence of Arymo ER 30 mg and MS Contin 30 mg and bioequivalence of two 15 mg strength Arymo ER tablets compared to one 30 mg strength tablet of MS Contin were demonstrated in Study 067-EG-012 as shown in the following table from page 6 of Dr. Nallani's review.

Table: Descriptive Statistics of morphine PK in Study 067-EG-012

	Morphine		
	EG-001 30 mg (n=60)	**MS Contin 30 mg (n=59)**	**EG-001 2x15 mg (n=61)**
AUC_∞ (ng•h/mL)	115.7 (26.1)	119.2 (29.1)	117.3 (27.1)
AUC_t (ng•h/mL)	111.9 (25.6)	113.9 (29.0)	112.3 (27.1)
C_{max} (ng/mL)	12.0 (33.5)	12.1 (33.3)	10.8 (33.1)
t_{max} (h)	4.50 (0.67, 6.00)	2.00 (0.67, 5.50)	4.50 (1.50, 8.00)
$t_{½}$ (h)	10.03 (23.6)	10.92 (21.2)	10.51 (23.9)

Bioequivalence of the 15 mg strengths of Arymo ER and MS Contin was not demonstrated in Study 067-EG-006, as described in the following table from page 7 of Dr. Nallani's review. The lower limit of the 90% confidence interval for the Cmax of morphine was 79%, just below the limit of 80%. This difference is not expected to have any clinical consequence.

Table: Descriptive Statistics of morphine PK in Study 067-EG-006.

	Morphine	
	EG-001 15 mg Tablet Fasting Conditions (n=64)	**MS Contin 15 mg Tablet Fasting Conditions (n=63)**
AUC_∞ (ng•h/mL)	47.3 (37.5)	48.0 (42.5)
AUC_t (ng•h/mL)	36.2 (34.0)	38.9 (39.0)
C_{max} (ng/mL)	4.41 (33.6)	5.35 (35.0)
t_{max} (h)	3.53 (1.50, 8.00)	2.00 (1.00, 6.00)
$t_{½}$ (h)	10.11 (47.7)	10.05 (50.0)

The effect of food was also evaluated in Study 067-EG-011. Using the 60 mg strength, there was a small increase in AUC, but the 90% confidence intervals were within the 80 to 125% bioequivalence range. Tmax was delayed to 6.5 hours, but as noted previously, this difference in Tmax would not have any clinical consequence for their product that will be dosed on an around-the-clock schedule. Arymo ER can be taken without regard to food.

As noted by Dr. Nallani, Since the BE studies established a satisfactory bridge between Arymo ER and MS Contin, the Applicant did not conduct any special population studies and would like to rely on the MS Contin product label.

Because the clinical pharmacology studies form the basis for relying on the efficacy and safety of MS Contin and no clinical efficacy studies were conducted, an OSIS audit was conducted for the BE study site and bioanalytical facilities ((b) (4)). The audit found no problems and the data may be relied upon for a regulatory decision.

Dr. Nallani reviewed the clinical abuse liability studies which collected both pharmacokinetic and pharmacodynamic assessments. These are reviewed below.

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

No new efficacy studies were conducted in support of this application. The Applicant is relying on the Agency's prior findings of efficacy and safety for MS Contin, having established an appropriate scientific link through the demonstration of bioequivalence. The details of the clinical pharmacology studies are provided in Section 5 of this memo.

8. Safety

Dr. Hariadi reviewed the safety data. The Applicant is primarily relying on the Agency's prior findings of safety for MS Contin. The clinical pharmacology studies with the to-be-marketed formulation were conducted in normal healthy volunteers who received naltrexone to block the opioid agonist effects of morphine. The primary question for this application is whether there are any formulation specific safety concerns such as difficulty swallowing the tablet.

The following is from Dr. Hariadi's review:

> A total of 442 healthy adult subjects from nine studies were exposed to Arymo/Egalet Morphine: 297 subjects received one single-dose and 145 subjects received between two and three doses. Overall, 400 subjects were exposed to the to-be-marketed formulation. This database is adequate to assess any formulation-related safety concerns, as agreed upon between the applicant and review division during the pre-NDA meeting (minimum of 100 subjects exposed to the to-be-marketed formulation).

There were no deaths and one serious adverse event of a spontaneous abortion that occurred 16 days after morphine administration in a 52 year old woman with a negative urine pregnancy test at screening and negative serum pregnancy test prior to study drug administration of a 60 mg dose of Arymo. The patient had received naltrexone to block the effects of morphine in this study. Subsequent serum pregnancy tests prior to the second study period were equivocal and then positive when repeated three days later. The event is unlikely related to study participation. Eleven subjects discontinued study participation early due to adverse events, including the subject with the one serious adverse event. The adverse events leading to discontinuation were primarily gastrointestinal. Details can be found in Dr. Hariadi's review.

The most common treatment emergent adverse events were somnolence, headache, dizziness, nausea, vomiting, abdominal discomfort and pruritus. In the intranasal abuse liabilty study, there were adverse events of nasal congestion and discomfort. The adverse events were consistent with exposure to morphine and naltrexone. There were no reports of choking upon swallowing the study medication.

9. Advisory Committee Meeting

A joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee was held on August 4, 2016. The committees discussed whether the data submitted by the Applicant were sufficient to support labeling of the product with the properties expected to deter abuse. The following has been reproduced from the meeting minutes:[3]

> ***Questions to the Committee:***
> 1. **DISCUSSION:** Please discuss whether there are sufficient data to support a finding that Arymo ER (morphine sulfate extended-release tablets) has properties that can be expected to deter abuse, commenting on support for abuse-deterrent effects for each of the three possible routes of abuse:
>
> a. Oral
> b. Nasal
> c. Intravenous
>
> ***Committee Discussion***: *It was the general consensus of the committee that there are sufficient data to support a finding of abuse-deterrent characteristics for the oral, nasal and intravenous routes of administration of Arymo ER. The committee stated that the phase one studies indicate extreme difficulty in reducing particle size and that Arymo ER could not easily be reduced to a size small enough for inhalation or snorting because of the hardness created through the manufacturing process. The committee also agreed that the small volume extraction showed limited removal of morphine for injection but large volume extraction studies did reveal the possibility of removal of relatively large amounts of morphine from the manufactured entity with some combinations of agents and conditions. Overall the committee stated that it appears*

[3] http://www fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM525207.pdf

that the nasal and intravenous abuse routes would be substantially reduced, along with the reduction in oral use by chewing. Please see the transcript for details of the committee discussion.

2. **VOTE:** If approved, should Arymo ER be labeled as an abuse-deterrent product by the oral route of abuse?

Vote Result: Yes: 16 No: 3 Abstain: 0

Committee Discussion: *The majority of the committee voted Yes, agreeing that Arymo ER should be labeled as an abuse-deterrent product by the oral route of abuse. Those who voted Yes stated that there was sufficient evidence and clear data that chewing of the product is reduced by its abuse-deterrent properties. Those who voted No stated that the term oral abuse-deterrent was too broad for them to agree with and a narrower claim such as not chewable would be more acceptable. Please see the transcript for details of the committee discussion.*

3. **VOTE:** If approved, should Arymo ER be labeled as an abuse-deterrent product by the nasal route of abuse?

Vote Result: Yes: 18 No: 1 Abstain: 0

Committee Discussion: *The majority of the committee voted Yes, stating that there was strong evidence that Arymo ER should be labeled as an abuse-deterrent product by the nasal route of abuse, and noted that this was supported through evidence of the challenges of physically manipulating the drug in addition to the human abuse potential studies. One committee member voted No, noting concerns about the large volume extraction possibility. Please see the transcript for details of the committee discussion.*

4. **VOTE:** If approved, should Arymo ER be labeled as an abuse-deterrent product by the intravenous route of abuse?

Vote Result: Yes: 18 No: 1 Abstain: 0

Committee Discussion: *The majority of the committee voted Yes, stating that Arymo ER should be labeled as an abuse-deterrent product by the intravenous route of abuse. One committee member voted No, noting concerns about the large volume extraction possibility. Please see the transcript for details of the committee discussion.*

5. **VOTE:** Should Arymo ER be approved for the 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?

Vote Result: Yes: 18 No: 1 Abstain: 0

Committee Discussion: *The majority of the committee voted Yes, stating that Arymo ER should be approved for the proposed indication. One committee member added that there are populations, such as palliative care patients, that are in need of long-term opioid use and that it would be nice to have other options in the marketplace. The committee member who voted No, suggested that more information is needed on the*

solvents used to test this product and noted concerns for the potential of abuse of Arymo ER with some solvents. Please see the transcript for details of the committee discussion.

10. Pediatrics

This application did not trigger the requirements for pediatric studies under the Pediatric Research Equity Act.

11. Other Relevant Regulatory Issues

Assessment of Abuse Deterrence

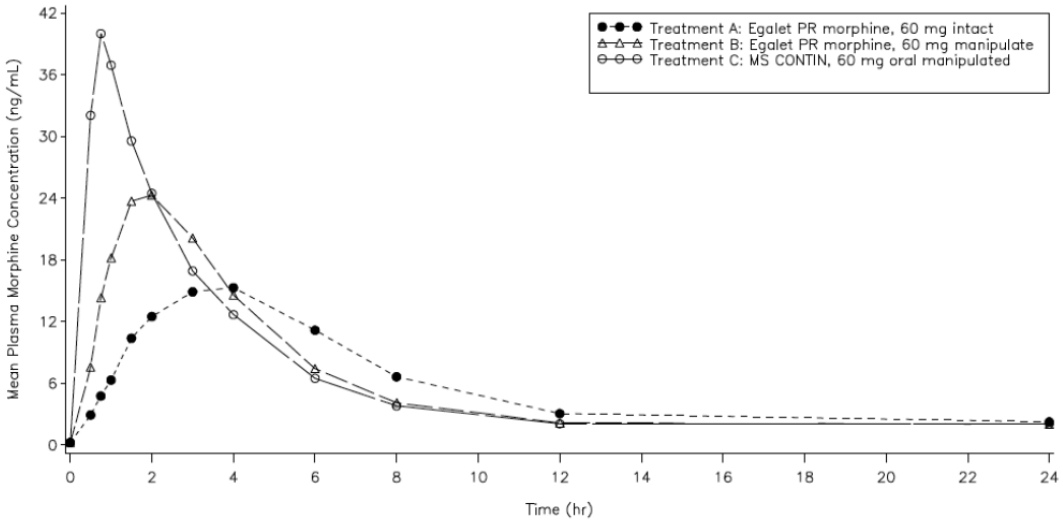
The Applicant conducted in vitro and in vivo studies to evaluate the abuse-deterrent properties of Arymo ER. The in vitro assessment was reviewed by Dr. Pavuluri and is described in Section 3 of this memo. The data support that Arymo ER appears to possess physical and chemical features that resist small volume extraction from intact and manipulated tablets, and resists syringing following manipulations. These findings are consistent with a conclusion that Arymo ER has abuse-deterrent features that will make abuse via injection route difficult. Two abuse liability studies were conducted to evaluate possible abuse-deterrent effects for the oral and intranasal routes of abuse.

Abuse Deterrence Properties for Oral Route of Administration

Study 067-EG-008 was a randomized, double-blind, triple-dummy, active- and placebo-controlled, four-way crossover study comparing manipulated and intact Arymo ER versus manipulated MS Contin following oral administration. Thirty-eight non-dependent recreational opioid users participated following successful completion of the naloxone challenge and the discrimination phase of the study. The morphine dose in the discrimination phase was 30 mg of immediate-release morphine sulfate. The treatments were Arymo ER 60 mg oral intact, Arymo ER 60 mg oral manipulated, MS Contin 60 mg oral manipulated, and placebo. The manipulated condition for Arymo ER was to cut a 60 mg tablet into pieces over three minutes and then it was administered orally directly from the vial and followed by 150 mL of juice. As an exploratory arm in 12 patients, Arymo ER was manipulated and mixed in the juice. As noted by Dr. Nallani in his review, cutting and further manipulating Arymo ER was able to better defeat the abuse-deterrent properties.

The extended-release profile of Arymo ER was defeated to a large extent by cutting the tablet and taking the tablet orally, as shown below in the figure from page 11 of Dr. Nallani's review and the following table from page 19 of Dr. Tolliver's review.

Figure : Mean Morphine Plasma Concentrations (ng/mL) vs. on Linear Scale- PK Population (N = 39)



Source: Figure 14.2.7.4.1

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)
Cmax (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
Tmax (hours)	Median	0.880	2.120	4.120
	Range	0.63, 4.13	0.88, 4.15	1.63, 6.13

The pharmacodynamic endpoints from Study 067-EG-008 are provided in the following table from page 20 of Dr. Tolliver's review. None of the scores are particularly high for these endpoints. The drug liking scores for crushed MS Contin, while clearly higher than for placebo, only reached an average of 73 on the bipolar scale.

Table 6. Descriptive Statistics for Treatments in Treatment Phase for Completer Population (N=38).

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

This clinical abuse potential study does not support a conclusion that Arymo ER can be expected to deter abuse by the oral route of administration. The results of this negative study will be described in the proposed labeling. (b) (4)

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The pivotal relative bioavailability study was referred for inspection. As noted in Dr. Nallani's review, the Office of Scientific Investigation "recommended accepting data without an on-site inspection as the site listed ((b) (4)) was recently inspected and the inspectional outcome was "No Action Indicated".

Abuse Deterrence Properties for Intranasal Route of Administration

As described in the review, the Applicant conducted a new clinical investigation that supports an expected reduction of abuse of Arymo ER by the intranasal route of administration due to physicochemical properties. As discussed above, Morphabond has 3 years of exclusivity, which is reflected in the Orange Book with code M-189, described as "labeling describing the expected reduction of abuse of single-entity extended-release morphine by the intranasal route of administration due to physicochemical properties."[4] This exclusivity expires on October 2, 2018, 3 years after the date of Morphabond's approval. During this 3-year period, any

[4] An application for a drug containing a previously approved active moiety is eligible for 3-year exclusivity if the approval of the application is supported by at least one (1) new (2) clinical investigation (other than a bioavailability study) (3) that is conducted or sponsored by the applicant and is (4) essential to the approval of the application. See sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the FD&C Act. The approval of an NDA or supplement to an NDA includes approval of labeling submitted in the NDA or supplement. 21 CFR 314.50.

subsequent 505(b)(2) application (or ANDA) that includes labeling describing the expected reduction of abuse of single-entity ER morphine by the intranasal route of administration due to physicochemical properties will be blocked from approval. Such exclusivity, however, does not block the approval of a subsequent 505(b)(2) application (or ANDA) that is not seeking approval of any exclusivity-protected condition(s) of approval (i.e., the condition(s) of approval for which new clinical investigations were essential). Arymo ER is not being approved for any exclusivity-protected condition of approval, including Morphabond's exclusivity-protected conditions of approval, i.e., Arymo ER is not being approved with labeling describing an expected reduction of abuse of single-entity extended-release morphine by the intranasal route of administration due to physicochemical properties. As currently labeled, Arymo ER is both safe and effective, and otherwise meets all the requirements for approval described in subsections (c) and (d) of section 505 of the Federal Food, Drug, and Cosmetic Act.

There are no other unresolved relevant regulatory issues.

12. Labeling

The proposed proprietary name, Arymo ER, was found acceptable. Carton and container labels were reviewed and the final labels found acceptable from a medication error prevention perspective. Labeling recommendations from the patient labeling team were implemented. OPDP has provided comments that were incorporated into the labeling. Labeling comments from the Division of Pediatric and Maternal Health were incorporated into the product labeling.

The labeling regarding the evaluation of the abuse-deterrent properties of Arymo ER is reproduced below from Section 9.2 of the package insert with comments regarding the selection of the language. Because of the exclusivity for Morphabond, as described above, there is no mention of the clinical pharmacology or human abuse potential studies of Arymo ER included in the labeling.

Agreed Upon Labeling	**Comment**
<u>Abuse Deterrence Studies</u>	
ARYMO ER is formulated with inactive ingredients that make the tablet more difficult to manipulate for misuse and abuse.	This represents common introductory language being used for this section.
To evaluate the ability of ARYMO ER to reduce the potential for misuse and abuse, a series of abuse-deterrent in vitro laboratory physical manipulation, chemical extraction, and syringeability studies was conducted. An oral pharmacokinetic study and an oral clinical abuse potential study were also conducted.	

Agreed Upon Labeling

In Vitro Testing

In vitro physical and chemical manipulation studies were performed to evaluate the ability of different methods to defeat the extended-release properties. The results of this testing demonstrated that ARYMO ER tablets, in comparison to morphine sulfate extended-release tablets, have increased resistance to cutting, crushing or breaking using a variety of tools. When subjected to a liquid environment, the manipulated ARYMO ER tablets form a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a hypodermic needle.

Comment

Because the in vitro testing demonstrated resistance to manipulation, particularly resistance to passage through a hypodermic needle, this language is an accurate reflection of relevant abuse-deterrent properties of the formulation.

Oral Pharmacokinetic Study

The pharmacokinetic profile of manipulated ARYMO ER was characterized following oral administration. The study was conducted in a randomized cross-over design. The pharmacokinetic profile of manipulated and intact ARYMO ER compared to crushed morphine sulfate extended-release was evaluated in 38 subjects after oral administration. The results are summarized in Table 1 and demonstrate that oral ingestion of manipulated ARYMO ER resulted in a higher C_{max}, but similar AUC, when compared to intact ARYMO ER. In addition, manipulated ARYMO ER had a lower C_{max} and longer T_{max} than crushed morphine sulfate extended-release tablets.

The description of this study accurately reflects the results, that there is loss of some of the extended-release characteristics of Arymo ER when taken orally after manipulation

Table 1: Results from Oral Pharmacokinetic Study

PK Parameter	ARYMO ER		Crushed Morphine Sulfate ER (n = 39)
	Manipulated (n = 38)	Intact (n = 38)	
C_{max} (ng/mL)			
Mean (SD)	28.7 (9.1)	17.8 (6.6)	42.3 (14.3)
Median (Range)	29.2 (12.5, 47.8)	16.7 (8.5, 32.3)	42.2 (14.2, 79.0)
T_{max} (h)			
Median (Range)	2.1 (0.9, 4.2)	4.1 (1.6, 6.1)	0.9 (0.6, 4.1)
$AUC_{0-\infty}$ (h*ng/mL)			
Mean (SD)	159.3 (36.8)	168.0 (53.6)	182.1 (49.9)
Median (Range)	157.1 (94.5, 215.3)	159.4 (80.9, 274.8)	185.5 (61.8, 284.1)

C_{max} = maximum observed plasma concentration; T_{max} = time to achieve the maximum observed plasma concentration; $AUC_{0-\infty}$ = area under the curve, zero to infinity

Agreed Upon Labeling

Oral Clinical Abuse Potential Study

An oral abuse potential study was conducted in 39 subjects who were non-dependent recreational opioid users; 38 subjects completed the study. Treatment arms included manipulated ARYMO ER 60 mg tablets (taken with juice), intact ARYMO ER 60 mg tablets (taken with juice), crushed 60 mg morphine sulfate extended-release tablets (mixed in juice), and placebo.

The study demonstrated that the oral administration of manipulated ARYMO ER resulted in a statistically lower mean drug liking score than the oral administration of crushed morphine sulfate extended-release tablets. However, the difference between manipulated ARYMO ER and crushed morphine sulfate extended-release tablets for Take Drug Again was not statistically significant, indicating that the difference in drug liking scores was not clinically meaningful.

These results are summarized in **Error! Reference source not found.**.

Table 2: Summary of Maximum Scores (E_{max}) for Drug Liking and Take Drug Again VAS[1] Following Oral Administration of Manipulated and Intact ARYMO ER and Crushed Morphine Sulfate Extended-Release in Non-Dependent Recreational Opioid Users

Parameter	ARYMO ER		Crushed Morphine Sulfate ER (n = 38)	Placebo (n = 38)
	Manipulated (n = 38)	Intact (n = 38)		
Maximum Drug Liking (E_{max})				
Mean (SD)	68.3 (12.3)	63.2 (10.1)	73.3 (9.8)	53.3 (7.8)
Median (Q1, Q3)	67.0 (61.0, 75.0)	62.0 (56.0, 68.0)	74.0 (68.0, 79.0)	50.0 (50.0, 52.0)
Take Drug Again (E_{max})				
Mean (SD)	62.9 (19.6)	54.8 (20.8)	70.1 (17.5)	51.0 (10.2)
Median (Q1, Q3)	61.5 (51.0, 71.0)	56.0 (50.0, 65.0)	68.0 (56.0, 80.0)	50.0 (50.0, 50.0)

[1] 100 point bipolar VAS (0=maximum negative response, 50=neutral response, 100=maximum positive response)

Comment

The results of this study are not consistent with an oral abuse deterrent effect, and have been included to alert prescribers to this finding.

Agreed Upon Labeling	Comment
Summary The in vitro data demonstrate that ARYMO ER has physicochemical properties expected to make abuse by injection difficult. Although the results of the oral human abuse potential study showed a difference in the Drug Liking endpoint, there was no statistically significant reduction in the response to Take Drug Again. Therefore, it cannot be concluded that ARYMO ER has physical and chemical properties that are expected to reduce abuse via the oral route. Abuse of ARYMO ER by injection, as well as by the oral and nasal routes, is still possible. Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of ARYMO ER on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.	This summary provides the positive and negative results from the evaluation.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval
- Risk Benefit Assessment

Based on the relative bioavailability study results comparing Arymo ER and MS Contin, it is reasonable to conclude that Arymo ER can rely on the Agency's previous findings of efficacy and safety for MS Contin. Adequate chemistry, manufacturing and controls information, and adequate biopharmaceutics data were submitted to support the application. No nonclinical studies were conducted and the Applicant provided adequate justification to support the safety of the excipients in the formulation. The pharmacokinetic data adequately describe the properties of the product relative to the listed drug, and in the fasted and fed states. There was an adequate in vitro evaluation of the physicochemical abuse-deterrent properties to support the proposed labeling. The results of the oral pharmacokinetic and oral human abuse liability study of manipulated Arymo ER, which do not support a likely oral abuse-deterrent effect, are provided in the labeling. Additionally, as discussed above and at the advisory committee meeting held August 4, 2016, the Applicant submitted data describing the successful human abuse potential study evaluating the intranasal administration of manipulated Arymo ER.[5]

[5] Materials from the advisory committee meeting can be found at: http://www fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm514372 htm

These data will not be included in labeling due to the exclusivity issues described in this memo, but the absence of this information does not render the product, as labeled, unsafe or ineffective.[6]

- Recommendation for Postmarketing Risk Management Activities

Arymo ER will be part of the Extended-Release and Long-Acting REMS.

- Recommendation for other Postmarketing Study Commitments

POSTMARKETING REQUIREMENTS UNDER 505(o)

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 must address at a minimum the following specific objectives:

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.

[6] Most of the reviews for the Arymo NDA were finalized before CDER decided whether the exclusivity-protected condition of approval could be omitted from the Arymo ER product labeling without rendering Arymo ER unsafe or ineffective. As noted in the text, CDER has decided that the omission of such information does not render Arymo ER, as labeled, unsafe or ineffective. To the extent some sentences in the underlying reviews could be read as stating otherwise, those reviews were finalized before closure on this issue was reached and some of the wording is not optimal. However, it is worth noting that this issue has been extensively considered and there is no disagreement regarding CDER's decision that Arymo ER can be approved as safe and effective as labeled.

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.

This study must address at a minimum the following specific objectives:

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.

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.

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.

3033-5 An observational study to validate measures of prescription opioid Substance Use Disorder and addiction in patients who have received or are receiving opioid analgesics for chronic pain.

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.

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.

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.

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.

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

(1) utilization of ARYMO ER 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 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 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.

3148-2 Conduct formal observational studies to assess whether the properties intended to deter misuse and abuse of ARYMO ER actually result in a meaningful decrease in misuse and abuse, and their related clinical outcomes, 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 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 Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data.*

3148-3 Analyze the polyethylene oxide (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.

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 polyethylene oxide (PEO) components (impurities/degradants) in (b) (4) when the product is consumed up to the MTDD of ARYMO ER.

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 polyethylene oxide (PEO) components (impurities/degradants) in (b) (4) when the product is consumed up to the MTDD of ARYMO ER.

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 polyethylene oxide (PEO) components (impurities/degradants) in (b) (4) when the product is consumed up to the MTDD of ARYMO ER.

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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

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 (crushed using the optimal method for smallest particle size), and pre-treated tablets (oven or microwave heating).

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.

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/s/

SHARON H HERTZ
01/09/2017