

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204223Orig1s000

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 # 204223 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: Morphine Sulfate Dosage Form: Injection (IV and/or IM) Strengths: 2 mg/ml, 4mg/ml, 5 mg/ml, 8 mg/ml, 10 mg/ml		
Applicant: Becton Dickinson Agent for Applicant (if applicable):		
Date of Application: 5/31/2012 Date of Receipt: 6/1/2012 Date clock started after UN:		
PDUFA Goal Date: 11/2/2013		Action Goal Date (if different): 10/30/2013
Filing Date: 7/31/2012		Date of Filing Meeting: 7/10/2012
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 5- New Formulation or New Manufacturer		
Proposed indication(s)/Proposed change(s): Morphine sulfate is a pure opioid agonist indicated for the management of pain not responsive to non-narcotic analgesics.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/> n/a		Resubmission after refuse to file? <input type="checkbox"/> n/a
Part 3 Combination Product? <input type="checkbox"/> n/a <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): n/a				
List referenced IND Number(s): n/a				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	√			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	√			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, 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</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	√			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		√		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	√			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>√</p>																		
<p>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)].</p>		<p>√</p>																		
<p>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)]?</p> <p><i>If you answered yes to any of the above 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</i></p>		<p>√</p>																		
<p>Is there unexpired exclusivity on the 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</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </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														<p>√</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm</p>		<p>√</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			√	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		√		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA only</i>)?</p>		√		
<p>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)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			√	

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

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

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			√	
If yes, BLA #				
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			√	
<ul style="list-style-type: none"> If yes, were all of them submitted on time? 			√	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			√	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			√	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	√			
<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?	√			with CMC
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)?	√			

<p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>		√		No clinical sites
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><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></p>	√			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><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></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	√			
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff: n/a</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff: July 3, 2012</i></p>			√	
	√		√	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, 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></p>		√		
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>			√	
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>			√	
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</p> <p><i>If no, request in 74-day letter</i></p>			√	
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>		√		
Proprietary Name	YES	NO	NA	Comment
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>		√		
REMS	YES	NO	NA	Comment
<p>Is a REMS submitted?</p> <p><i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i></p>		√		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	√			
Is the PI submitted in 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>			√	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	√			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)	√			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	√			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
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?				

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

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) 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)	√			OSI for PK Studies
<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):		√		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s):		√		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		√		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 10, 2012

BLA/NDA/Supp #: NDA 204223

PROPRIETARY NAME: n/a

ESTABLISHED/PROPER NAME: morphine sulfate, USP

DOSAGE FORM/STRENGTH: injection/2 mg/mL, 4 mg/mL, 5 mg/mL, 8 mg/mL, and 10 mg/mL

APPLICANT: Becton, Dickinson, and Company

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): indicated for the Management of pain not responsive to non-narcotic analgesics.

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Christopher Hilfiger	y
	CPMS/TL:	Parinda Jani	y
Cross-Discipline Team Leader (CDTL)	Ellen Fields		
Clinical	Reviewer:	Ellen Fields	y
	TL:	Ellen Fields	y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Srikanth Nallani	y
	TL:	Yun Xu	y
Biostatistics	Reviewer:	N/A	
	TL:	Dionne Price	y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Carlic Huynh	y
	TL:	Dan Mellon	y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Julia Pinto	y
	TL:	Presad Peri	y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Elisbeth Chikhale	y
	TL:	John Duan	n
CMC Labeling Review	Reviewer:		n
	TL:		n
Facility Review/Inspection	Reviewer:	Vibhakar J Shah	
	TL:	Tara R Goen	
OSE/DMEPA (proprietary name)	Reviewer:	Vicki Borders-Hemphill	n
	TL:	Jamie Wilkins	n
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	Stephen Sun	Y
	TL:	Michael Klein	n
Other reviewers			
Other attendees	Sharon Hertz, Deputy Division Director		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues: Non-Clinical reference products other than RLD. Sponsor resubmitted non-Clinical section</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: no clinical efficacy/safety studies See Clinical Pharmacology section</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p>If no, for an NME NDA or original BLA , include the</p>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

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

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: File</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments: none	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Sharon Hertz, MD 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: GRMP timelines will be observed.	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): SRPI Label Issues <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review:

	<ul style="list-style-type: none"> notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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
10/30/2013

505(b)(2) ASSESSMENT

Application Information		
NDA # 204223	NDA Supplement #: S- 0000	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: Morphine Sulfate Dosage Form: Injection Strengths: 2mg/ml, 4mg/ml, 5mg/ml, 8 mg/ml, 10 mg/ml		
Applicant: Becton, Dickinson and Co.		
Date of Receipt: June 1, 2012		
PDUFA Goal Date: April 1, 2013		Action Goal Date (if different): N/A
RPM: Christopher Hilfiger		
Proposed Indication(s): the management of pain not responsive to non-narcotic analgesics.		

GENERAL INFORMATION

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

YES NO

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



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

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

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 202515 - Hospira Inc's Morphine Sulfate Injection 2 mg/mL, 4 mg/mL, 8 mg/mL, 10 mg/mL and 15 mg/mL	FDA's previous finding of safety and effectiveness - clinical and nonclinical
NDA 019999 -Meridian Medical Technology's Morphine Sulfate Injection, 15 mg/mL	FDA's previous finding of safety and effectiveness - clinical and nonclinical

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

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The sponsor conducted:

1. **AN OPEN-LABEL, RANDOMIZED, 2-WAY CROSSOVER STUDY TO ASSESS THE COMPARATIVE BIOAVAILABILITY OF MORPHINE SULFATE 10 MG ADMINISTERED INTRAMUSCULARLY FROM A BD PREFILLED SYRINGE (TEST) AND THE MERIDIAN MORPHINE AUTO-INJECTOR (REFERENCE) IN HEALTHY SUBJECTS**
2. The Sponsor did not conduct any study with the IV formulation and requested Biowaiver for the proposed IV route of administration.

RELIANCE ON PUBLISHED LITERATURE

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

YES NO

If "NO," proceed to question #5.

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

YES NO

If "NO", proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

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

YES NO

RELIANCE ON LISTED DRUG(S)

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

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

YES NO

If "NO," proceed to question #10.

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

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Hospira Inc's Morphine Sulfate Injection 2 mg/mL, 4 mg/mL, 8 mg/mL, 10 mg/mL and 15 mg/mL	NDA 202515	y
Meridian Medical Technology's Morphine Sulfate Injection, 15 mg/mL	NDA 019999	y

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

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

N/A YES NO

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

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

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

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

YES NO

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

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

b) Approved by the DESI process?

YES NO

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

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

c) Described in a final OTC drug monograph?

YES NO

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

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

d) Discontinued from marketing?

YES NO

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

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

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

YES NO

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

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

This application provides for both the IV and IM route of administration for the same drug substance - Morphine Sulfate. The RLDs (NDAs 19999 and 202515) have either an IM (NDA 19999) route of administration or IV (NDA 202515) route of administration.

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

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

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

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

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

YES NO

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

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A YES NO

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

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

Pharmaceutical equivalent(s):

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

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

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

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

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

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

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

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

Pharmaceutical alternative(s): ER Capsules (NDAs 20616, 21260 + multiple generics); Injection (NDAs 18565, 19916 + multiple generics); Oral Solution (NDAs 201517, 22195 + multiple generics); ER Tablets (NDA 19516 + multiple generics); and IR Tablet (NDA 22207)

PATENT CERTIFICATION/STATEMENTS

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

Listed drug/Patent number(s):

No patents listed proceed to question #14

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

YES NO

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

Listed drug/Patent number(s):

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

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

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

Patent number(s):

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

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

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

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

(a) Patent number(s):

- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

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

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

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

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

Date(s):

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

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

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

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

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
10/30/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	Morphine Sulfate Injection, Preservative Free, CII
Applicant	Becton Dickinson Rx Inc.
Application/Supplement Number	NDA 204223
Type of Application	Original
Indication(s)	For the management of pain not responsive to non-narcotic analgesics
Established Pharmacologic Class ¹	Opioid Agonist
Office/Division	ODE II/DAAAP
Division Project Manager	Christopher Hilfiger
Date FDA Received Application	May 2, 2013
Goal Date	November 1, 2013
Date PI Received by SEALD	October 23, 2013
SEALD Review Date	October 23, 2013
SEALD Labeling Reviewer	Abimbola Adebawale
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- NO** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment: *The top, left and right HL margins are greater than ½ inch. Decrease them to ½ inch margins.*

The font size is 7-point which is less than the minimum 8-point font. Increase the font size to 8-point type.

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *HL length is > one-half page. DAAAP will grant a waiver in the approval letter.*

- NO** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: *The following headings in HL are not in the center of the horizontal line: Indications and Usage, Dosage and Administration, Dosage Forms and Strengths, Contraindications, Warnings and Precautions, Adverse Reactions, Drug Interactions, and Use in Specific Populations. Center them.*

The horizontal lines are shorter on the right side of the headings compared to those on the left side. Each horizontal line should extend over the entire width of the column.

- NO** 4. White space must be present before each major heading in HL.

Comment: *There is no white space before the Warnings and Precautions heading in HL. Insert.*

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

Selected Requirements of Prescribing Information

YES

6. Section headings are presented in the following order in HL:

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

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

NO

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment: *There are two separate horizontal lines instead of one complete horizontal line separating the HL and TOC.*

HIGHLIGHTS DETAILS

Highlights Heading

YES

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

Comment:

Highlights Limitation Statement

NO

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment: *The bolded HL Limitation statement should read as " These highlights do not include all the information needed to use MORPHINE SULFATE INJECTION safely and effectively. See full prescribing information for MORPHINE SULFATE INJECTION" instead of (b) (4)*

Product Title

YES

10. Product title in HL must be **bolded**.

Comment: *The Product Title currently reads as (b) (4) " instead of "Morphine Sulfate Injection Preservative Free, for intravenous or intramuscular use, CII" as per 21CFR 201.57(a)(2) (i.e. Product Title includes the proprietary name, established name of the drug, dosage form, route of administrations and the controlled*

Selected Requirements of Prescribing Information

substance symbol). Also consider removing [REDACTED] ^{(b) (4)} ” from the product title if it is not part of the established name.

Initial U.S. Approval

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

Comment:

Boxed Warning

- N/A** 12. All text must be **bolded**.

Comment:

- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(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, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Selected Requirements of Prescribing Information

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

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

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

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

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

Comment:

Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *The bolded revision date at the end of HL should read as “Revised: November 2013” instead of [REDACTED] ^{(b)(4)}.” The revision date should also be aligned to the right instead of the left.*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.
Comment:
- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.
Comment:
- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment: Subsection heading 2.5 is missing from both the TOC and the FPI. Subsection heading 5.14 “Special Risk Groups” in the FPI is missing from the TOC. Match the TOC and FPI subsection heading.
- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment:
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:
-

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:

Selected Requirements of Prescribing Information

YES

38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

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

Comment:

N/A

39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES

40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see *Warnings and Precautions (5.2)*]”.

Comment:

N/A

41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

Selected Requirements of Prescribing Information

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A

42. All text is **bolded**.

Comment:

N/A

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

Comment:

N/A

44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A

45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

N/A

46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

N/A

47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

Patient Counseling Information

N/A

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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

/s/

ABIMBOLA O ADEBOWALE
10/23/2013

ERIC R BRODSKY
10/23/2013

I agree. Eric Brodsky, SEALD labeling team leader, signing for Laurie Burke, SEALD Director.

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

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

Memorandum

Date: October 8, 2013

To: Chris Hilfiger
Senior Regulatory Project Manager
Division Anesthesia, Analgesia, and Addition Products (DAAAP)

From: Eunice Chung-Davies, Pharm.D., Regulatory Review Officer
Division of Advertising and Promotional Review 2
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 204233
OPDP labeling comments for morphine sulfate injection CII

In response to DAAAP's September 26, 2013, consult request, OPDP has reviewed the draft Prescribing Information (PI) for morphine sulfate injection CII. Comments on the proposed PI are based on the version available at an EDR link sent via email from Chris Hilfiger (RPM) on September 25, 2013, entitled "Labeling compare CR to resubmission.doc". Please note that OPDP's comments on the proposed PI are provided directly on the marked version below.

If you have any questions regarding the PI, please contact Eunice Chung-Davies at 301-796-4006 or eunice.chung-davies@fda.hhs.gov.

Thank you for the opportunity to comment!

Enclosure: Marked up PI

16 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/

EUNICE H CHUNG-DAVIES
10/08/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: March 14, 2013

Reviewer(s): Vicky Borders-Hemphill, Pharm.D.
Division of Medication Error Prevention and Analysis

Team Leader: Jamie Wilkins Parker, Pharm.D.
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Morphine Sulfate Injection, USP, 2 mg/ml, 4 mg/ml,
5 mg/ml, 8 mg/ml, and 10 mg/ml

Application Type/Number: NDA 204223

Applicant/sponsor: Becton, Dickinson and Company

OSE RCM #: 2012-2115

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

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1 INTRODUCTION

This review evaluates the proposed container/blister labels and carton and package insert labeling for Morphine Sulfate Injection, USP submitted under NDA 204223 for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

Morphine Sulfate Injection, USP, is an opioid agonist indicated for the management of pain not responsive to non-narcotic analgesics.

Currently, multiple formulations of morphine sulfate are marketed in the United States. Morphine sulfate is available in oral and injectable dosage forms. Currently marketed injectable morphine products are as follows:

- Single use 1 ml Carpuject (2 mg/ml, 4 mg/ml, 8 mg/ml, 10 mg/ml and 15 mg/ml) and 1 ml iSecure prefilled (2 mg/ml, 4 mg/ml, 8 mg/ml, 10 mg/ml and 15 mg/ml) syringes with Luer lock adapter for direct intravenous administration.
- Single use 10 mg/0.7 ml Auto-Injector for intramuscular administration using a spring-driven injection mechanism
- Ampules and single use vials [1 mg/2 ml and 5 mg/10 ml (0.5 mg/ml), 2 mg/2 ml and 10 mg/10 ml (1 mg/ml)] for administration by intravenous, epidural or intrathecal routes.
- Single dose Patient Controlled Analgesia vials [15 mg/30 ml (0.5 mg/ml), 30 mg/30 ml (1 mg/ml), and 150 mg/30 ml (5 mg/ml)] for use with infusion pump set and vial injector for intravenous administration
- Highly concentrated large volume ampules [200 mg/20 ml (10 mg/ml) and 500 mg/20 ml (25 mg/ml)] intended for continuous epidural or intrathecal infusion via a controlled microinfusion device; not recommended for single dose intravenous, intramuscular, or subcutaneous administration.

1.2 REGULATORY HISTORY

On May 31, 2012, the Applicant submitted a 505(b)(2) New Drug Application for Morphine Sulfate Injection, USP (NDA 204223) to be supplied as single use 1 mL pre-filled disposable syringes (2 mg/mL, 4 mg/mL, 5 mg/mL, 8 mg/mL, and 10 mg/mL) for intramuscular or direct intravenous administration. The application references two approved drug applications. One application held by Hospira, NDA 202515, Morphine Sulfate Injection, USP (2 mg/mL, 4 mg/mL, 8 mg/mL, 10 mg/mL and 15 mg/mL) is only to be administered by the intravenous route using a pre-filled syringe and was approved November 14, 2011. The other application held by Meridian Medical Technology is only to be administered by the intramuscular route using a pre-filled syringe, NDA 019999, Morphine Sulfate Injection (10 mg/0.7 mL) was approved on July 12, 1990.

1.3 PRODUCT INFORMATION

The following product information is provided in the August 21, 2012, labeling submission.

- Active Ingredient: morphine sulfate
- Indication of Use: indicated for the management of pain not responsive to non-narcotic analgesics
- Route of Administration: intramuscular or direct intravenous injection
- Dosage Form: injection
- Strength(s): 2 mg/mL, 4 mg/mL, 5 mg/mL, 8 mg/mL, and 10 mg/mL
- Dose and Frequency:
 - Direct Intravenous: usual starting dose in adults is 0.1 mg to 0.2 mg per kg every 4 hours as needed for pain; intravenous bolus: The initial dose of morphine should be 2 mg to 10 mg/70 kg of body weight, infused slowly every ^(b)₍₄₎ 4 hours as needed for pain;
 - Intramuscular: initial dose for a 70 kg individual is 10 mg (adjusted based on body weight, known tolerance, patient condition, and concomitant medications); Subsequent doses may be administered every 4 hours
- How Supplied: 1 mL pre-filled disposable syringes with Luer lock adapter
- Storage: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature.] Protect from light.
- Container and Closure System: 1 syringe/blister as a carton of twenty-four (24) syringes for each strength

2 METHODS AND MATERIALS REVIEWED

The Division of Medication Error Prevention and Analysis (DMEPA) searched the FDA Adverse Event Reporting System (FDA AERS) (Appendix A) for morphine sulfate injection medication error reports. Also, DMEPA reviewed the morphine sulfate injection, USP container labels and package insert labeling submitted by the Sponsor.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA AERS using the strategy listed in Table 1. Dates were truncated based upon the date of the last DMEPA review (OSE RCM# 2011-214).

Table 1: FDA AERS Search Strategy	
Date	July 16, 2011 through December 10, 2012
Drug Names	Product name 'Morphine'
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues (HLT) Product Label Issues (HLT) Product Quality Issues (NEC) (HLT)

The FDA AERS database search identified 147 cases. Each report was reviewed for relevancy and duplication. The following table lists cases (n=142) not included in the final analysis upon individual review.

Reason not included	# of cases (n=142)
Lacked sufficient information to determine if a medication error occurred	12
Lacked sufficient information to determine route of morphine sulfate administration	36
Described an adverse event or medication error associated with another product other than morphine sulfate injection	25
Described a medication error associated with oral morphine sulfate	56
Involved an error associated with improperly programmed morphine patient controlled analgesic pump or continuous ambulatory drug delivery device	5
Involved morphine diversion from patient controlled analgesic pump	1
Described morphine infusion dose omission	1
Described concomitant use of opioids, which included morphine sulfate injection, resulting in opioid overdose	1
Described intentional overdose associated with morphine sulfate injection	1
Administration of expired morphine sulfate injection via infusion	1
Described inadvertent soft-tissue injection with morphine sulfate during a refill of an implanted drug delivery device	2
Described a faxed medication order interpretation error	1

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, DMEPA evaluated the following:

- Container Labels submitted March 7, 2013 (Appendix B)
- Blister Labeling submitted March 7, 2013 (Appendix C)
- Carton Labeling submitted May 31, 2012 (Appendix D)

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA previously reviewed container labels, and carton and package insert labeling (RCM #2011-214) submitted with the application held by Hospira, NDA 202515, Morphine Sulfate Injection, USP. DMEPA's recommendations were implemented by the Sponsor. NDA 202515, Morphine Sulfate Injection, USP, is one of the reference listed drugs for the subject of this review therefore the recommendations made at that time will be considered for this review.

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FDA AERS search and the risk assessment of container labels and carton and package insert labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, two morphine sulfate injection, USP medication error cases remained for our detailed analysis. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter.²

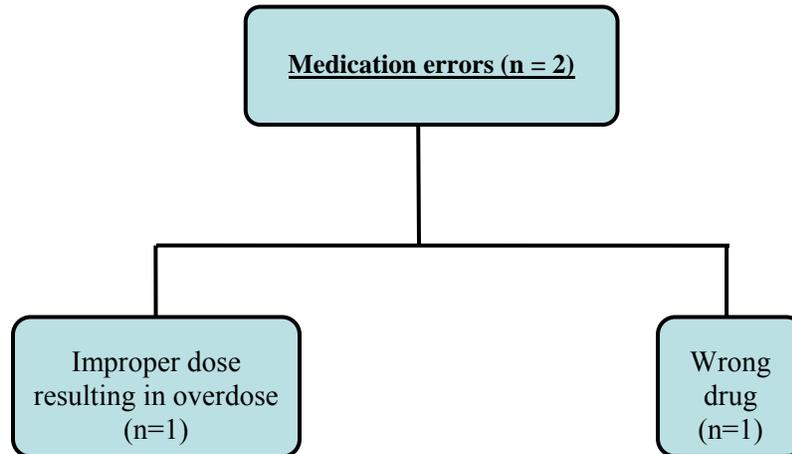
Figure 1 provides a stratification of the number of cases included in the review by type of error. Appendix E provides listings of all case numbers for the cases summarized in this review and contains a more detailed listing of the cases.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

Figure 1.

Morphine sulfate injection medication errors (n = 2) categorized by type of error



○ **Improper dose resulting in overdose (n=1)**

This case describes a patient being operated on with total intravenous and epidural anesthesia. Morphine at a dose of 1 mg/mL (total 100 mL) was added to the epidural pump containing bupivacaine and fentanyl. The patient experienced deterioration in awareness levels, arterial oxygen desaturation, arterial hypotension, and orotracheal intubation. The patient was transfer to the ICU with mechanical ventilation and intravenous vasoactive amines administered. Ultimately, the patient recovered from this medication error of improper dose resulting in overdose.

○ **Wrong drug (n=1)**

This case described the purchase of morphine preservative free (PF) 1 mg/mL, 2mL syringes (intravenous use only, not for epidural or intrathecal routes) compounded from (b) (4) as a substitute for Astramorph (morphine PF) 1 mg/mL, 2mL ampules (for intravenous, epidural or intrathecal routes). The syringes were stocked in automated dispensing machines in surgery, intensive care, and post surgical units but no doses were administered to patients.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

One case described a patient who received 100 mL of 1 mg/mL of morphine sulfate via an epidural pump as the result of a medication administration error. The morphine dose administered is usually given for an intravenous PCA pump. The cause of the wrong route of administration was not provided in the case narrative. It is not clear if the patient was supposed to receive the administered dose of morphine via a patient controlled intravenous analgesic pump or if the patient was supposed to receive an epidural dose of morphine via the epidural pump. It is not clear if the administered dose of morphine came from a pharmacy prepared syringe for the intravenous PCA pump or if the morphine dose

was pulled directly from a highly concentrated large volume ampule which states on the label that it is for neuraxial administration in continuous microinfusion device. Thus, it is undetermined whether this case could have been avoided with label and labeling modifications.

The other case described hospital procurement of the wrong morphine sulfate injection product. Preservative free morphine sulfate 1 mg/mL, 2 mL syringes, compounded by (b) (4), were purchased to replace Astramorph 1 mg/mL, 2 mL ampules. The procured syringes were not indicated for epidural or intrathecal use but were inadvertently made available on surgical and post surgical units but subsequently removed. No patients received the medication due to the label and labeling statements.

We assessed the proposed container labels, carton labeling, and package insert labeling for Morphine Sulfate Injection, USP submitted under NDA 204223. Since this application references two approved drug applications (NDA 202515 held by Hospira and NDA 019999 held by Meridian Medical Technology), we aimed to harmonize the proposed labels and labeling with the already approved products. We noted this proposed product contains the inactive ingredient edetate disodium. The inactive ingredient edetate disodium should not be administered via epidural or intrathecal routes. Thus, this product should not be administered via epidural or intrathecal routes and healthcare providers should be alerted that these routes are not appropriate. We also identified other areas of improvement to important information on the container label and blister, carton, and insert labeling which are listed below. Many of the recommendations for the container label aim to reduce clutter on the small container label of the syringe while including pertinent information to mitigate risk of medication errors. For example, although the container is missing the statement “Not for epidural or intrathecal use” as required by the Morphine Sulfate Injection, USP monograph, the container label may adhere to 21 CFR 201.10(i)(1), which states “A drug packaged in a container too small or otherwise unable to accommodate a label with sufficient space to bear the information required for compliance with section 502(e)(1) (A)(ii) and (B) of the act shall be exempt from compliance with those clauses: Provided that (1) the labels bears: (i) the proprietary name of the drug; (ii) the established name, if such there be, of the drug; (iii) an identifying lot or control number; and (iv) the name of manufacturer packer or distributor of the drug; and appears on the carton or other outer container or wrapper”. However, one of our recommendations is to increase the prominence of the proper route of administration. We provide label and labeling recommendations in Section 5 to address these concerns.

- Statements on container labels which contribute to clutter or detract from the established name and strength.
- Prominence of the milligram per milliliter (mg/mL) strength statement.
- Insert labeling instructions to harmonize with the other intramuscular and direct intravenous morphine products, and to provide clarity and reduce redundancy in the dosage and administration section. Specifically, we suggest removing instructions for doses given via intravenous infusion to avoid the suggestion that the 1 mL syringe be used for the preparation of a controlled morphine infusion. The intravenous infusion instructions were also deleted from the insert labeling for NDA 202515 which covers 1 mL single use carpuject and iSecure syringes.

Also, we note and defer to the Clinical reviewer if [REDACTED] (b) (4), should be deleted from the labeling. [REDACTED] (b) (4)

In addition, we note Section 2.3 Direct Intravenous Injection and section 2.8 Intramuscular Injection contain text that has been deleted from NDA 202515 and NDA 019999, and defer to clinical for their assessment.

4 CONCLUSIONS

DMEPA concludes that the proposed container label and blister and carton labeling can be improved to increase the readability and prominence of important information on the label to promote safe use of these products. We request the recommendations for the container labels in Section 5 be communicated to the Sponsor prior to approval.

5 RECOMMENDATIONS

Comments to the Division:

DMEPA provides the following comments for consideration by the review division prior to approval of the NDA. The insert labeling comments were based upon a review of the insert labeling for NDA 202515 which was approved on November 14, 2011.

A. Insert Labeling

1. Revise section 2.3 (Direct Intravenous Injection), provide instructions for direct intravenous injection and delete instructions that refer to doses given using a controlled infusion device as follows:

Parenteral products should be inspected for particulate matter and discoloration prior to administration. The usual starting dose in adults is 0.1 mg to 0.2 mg per kg every 4 hours as needed to manage pain. Administer the injection slowly.

[REDACTED] (b) (4)

2. Consider if section 2.4 (Intramuscular Injection) dosing instructions can be revised for clarity and to reduce redundancy similar to:

The initial intramuscular dose for a 70 kg (154 lbs) individual is 10 mg.

(b) (4)



NOTE: If the intramuscular dose per kilogram has been determined from clinical studies, we recommend that the applicant provide the intramuscular weight based dose as the number of milligrams per kilogram (mg/kg) instead of as 10 mg per 70 kilogram patient to make consistent with the intravenous weight based dose given per [one] kilogram.

- 3.

(b) (4)



Comments to the Applicant

DMEPA provides the following recommendations to be implemented prior to approval of the NDA:

- B. General Comments for all container labels, and blister and carton labeling

1. Revise the font of the “mg/mL” in the strength statement to be of equal prominence with that of the corresponding numeric strength to clarify that the number in the shaded area represents the strength of the product.
2. If the circle presentation does not allow the “mg/mL” statement to be adequately presented then the format should be revised to a boxed format. A boxed format would require revising the shaded circle surrounding the strength statement to appear as a shaded box. For example:

<div style="background-color: #90EE90; display: inline-block; padding: 2px 5px;">2 mg/mL</div>	<div style="background-color: #90EE90; display: inline-block; padding: 2px 5px;">2 mg/mL</div>
--	--

3. Consider revising the color scheme for the 5 mg/mL product to better differentiate this strength from the 4 mg/ml and 8 mg/mL, as the shades of (b) (4) currently used are similar and could cause confusion between the strengths.
4. Relocate the scheduled drug designation (CII) further away from the established name on the blister and carton labeling. (does not apply to the syringe container label) Ensure there is adequate white space between the established name and strength and the CII designation so that the CII designation does not interfere with the readability of these other statements. Additionally, consider reducing the font size of the CII designation to help decrease its prominence in relation to the established name and strength presentation.
5. Delete the statement “(b) (4)” from the principal display panel
6. Remove the word (b) (4) from the route of administration statement “For IM or (b) (4) IV use” to remove the undefined terminology. If space permits, revise the “IV” and “IM” abbreviations so that the route of administration appears as: “For Intramuscular or Intravenous use”.

C. Syringe Container Label

1. Your proposed syringe is made of clear glass and the current location of the barcode decreases the readability of the dosing panel. Relocate the bar code on the container labels so that the horizontal lines of the bar code are not visible and can not lead to confusion when viewing the dosing panel. Relocating the barcode will help to improve readability of the dosing panel when looking through the clear dosing panel of a label syringe.
2. Identify the expiration date of the product by preceding the expiration date with the abbreviation “Exp”.

3. Consider increasing the font size of the route of administration statement and placing it on white background to increase the prominence of the proper route of administration.
4. If space permits, consider increasing the font size of the statement “1 mL Single use” and placing it on white background to increase the prominence on the container label.
5. Delete “(b) (4)” from the principal display panel to reduce clutter on the container label as the requirement was removed per Federal Register Final Rule effective April 2, 2002 which amends 21 CFR Part 201 and 369 (67 FR 4904 document number 02-2548).

D. Blister Labeling

1. If space permits, revise the abbreviations “IV” and “IM” on the blister carton labeling so that the statement “For IM or (b) (4) IV use” appears in title case and reads “For Intramuscular or Intravenous use”. The abbreviation “IV” is often misinterpreted as “international units”, the “roman numeral 4”, or “intrajugular” as noted by the Institute of Safe Medication Practices and not permitted in patient records by the Joint Commission.² Relocate the correct route of administration statement “For IV or IM use” before the negative route of administration statement “NOT for intrathecal or epidural use”.
2. Delete the statement “(b) (4)” from the principal display panel to reduce clutter on the blister label as the requirement was removed per Federal Register Final Rule effective April 2, 2002 which amends 21 CFR Part 201 and 369 (67 FR 4904 document number 02-2548).

If you have further questions or need clarifications, please contact the OSE Regulatory Project Manager, Mark Liberatore, at 301-796-2221.

² ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations <http://www.ismp.org/Tools/errorproneabbreviations.pdf> ; cited September 20, 2011.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

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

APPENDIX E: CASE NUMBERS, VERSION, AND DETAILS OF CASES DISCUSSED IN THIS REVIEW

Case #	Vrsn	FDA Recd Date	Narrative
8475766	1	3/26/2012	<p>A 49-year-old man developed severe respiratory depression following an inadvertent overdose of epidural morphine. The man underwent a pulmonary lobectomy for lung carcinoma. He was operated on with total IV and epidural anaesthesia, with a catheter inserted at level T6-T7. Pain was controlled with an epidural perfusion of bupivacaine and fentanyl via patient-controlled analgesia, associated to IV paracetamol [acetaminophen] and dexketoprofen. Due to shoulder pain during the first few hours, morphine was added to the epidural perfusion (3mg in 250mL). Dipyrone was prescribed as a rescue analgesic. Twelve hours after being moved to the ward, he displayed a deterioration in awareness levels, arterial oxygen desaturation, and arterial hypotension. Orotracheal intubation was performed and the man was transferred to the ICU with mechanical ventilation and IV vasoactive amines. Once the solution containing bupivacaine, fentanyl and morphine had run out, it was realised that he had mistakenly been connected to the PCA epidural pump, receiving a perfusion of morphine 1 mg/mL (the dose typically used for IV PCA), of which approximately 100mL had been infused. The epidural perfusion was withheld. Naloxone was initiated and, after 12 hours, mechanical ventilation was discontinued. At last observation, he showed no signs of further problems.</p>
8510048	1	4/10/2012	<p>Due to the shortage of Astramorph (morphine PF) 1 mg/mL 2mL amps, we had to purchase morphine PF 1 mg/mL 2mL syringes compounded from Pharmedium. We received this order and stocked syringes in our automated dispensing machines for use in the surgery wing, the ICU, and one of the postsurg units. We went to place a second order through Pharmedium's electronic order system, and this item came up with a warning message "not for epidural or intrathecal use." We immediately pulled the product from our dispensing machines. No doses were administered to patients, but the primary use for this product in our facility is for epidural administration (& less commonly intrathecal).</p>

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/s/

BRENDA V BORDERS-HEMPHILL
03/14/2013

JAMIE C WILKINS PARKER
03/14/2013

SCOTT M DALLAS
03/14/2013

MEMORANDUM

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

DATE: December 3, 2012

TO: Robert A. Rappaport, MD
Director, Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II

FROM: Young Moon Choi, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations;

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 204-223, Morphine sulfate
prefilled syringe

At the request of the Division of Clinical Pharmacology 2, Office of Clinical Pharmacology, the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted an audit of the clinical and analytical portions of the following bioequivalence study:

Study Number: MED-11-PREFL01

Study Title: An Open-Label, Randomized, 2-Way Crossover Study To Assess The Comparative Bioavailability Of Morphine Sulfate 10 mg Administered Intramuscularly From A BD Prefilled Syringe (Test) And The Meridian Morphine Auto-Injector (Reference) In Healthy Subjects

Clinical Site: PRA Clinical Pharmacology Center,
Lenexa, KS

Analytical Site: [REDACTED] (b)(4)

The inspection of the clinical portion of the study was conducted at PRA Clinical Pharmacology Center, Lenexa, KS, by Ms. Vickie Kanion, an ORA investigator of KAN-DO, from 10/31/2012 to 11/2/2012. Ms. Vickie Kanion audited records pertinent to study MED-11-PREFL01 and collected reserve samples. She did not observe any objectionable conditions and no Form FDA-483 was issued at the close of clinical site inspection.

The inspection of the analytical portion of the study was conducted at [REDACTED] (b)(4). [REDACTED] (b)(4), an ORA investigator of [REDACTED] (b)(4), and Dr. Young Moon Choi, a pharmacologist of DBGLPC, participated in the inspection. The inspection team audited all study-related records, including notebooks and source data, and did not observe any objectionable conditions and no Form FDA 483 was issued at the close of the analytical site inspection.

CONCLUSION:

This reviewer recommends that the data from the study MED-11-PREFL01 are acceptable for your review.

Final Classification:

NAI - Clinical Site: PRA Clinical Pharmacology Center, Lenexa, KS,
FEI: 3005234558

NAI - Analytical Site: [REDACTED] (b)(4)

CC:

DBGC: Taylor/Haidar/Skelly/Cho/Choi/Dejernett/CF

DGP2: Sahajwalla/Nallani

DAAAP/ODE II/CDER: Hilfiger

KAN-DO: Kanion/Bromley/Bous

Draft: YMC 12/3/2012

Edit: JC 12/4/2012;SHH 12/7/2012

OSI: File # 6356; O:\BIOEQUIV\EIRCOVER\204223Bec Mor.doc

FACTS: 1425907

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/s/

YOUNG M CHOI
01/09/2013

SAM H HAIDAR
01/10/2013

WILLIAM H TAYLOR
01/10/2013



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

Date: August 16, 2012

To: Bob Rappaport, MD, Director
Division of Analgesics, Anesthesia, and Addiction Products (DAAAP)

Through: Michael Klein, PhD, Director
Controlled Substance Staff

From: Stephen Sun, MD, Medical Officer
Controlled Substance Staff

Subject: **Application:**
Morphine sulfate (NDA204223) Injection
Proposed Indication:
Management of pain not responsive to non-narcotic analgesics
Dosages:
2 mg/mL, 4 mg/mL, 5 mg/mL, 8 mg/mL, 10 mg/mL as single-use pre-filled syringe for intramuscular and intravenous use
Sponsor:
Becton Dickinson and Company

Materials reviewed: Becton Dickinson and Company. New Drug Application, #204223. Sections 2.4, 2.6, 2.7.

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I. Summary

A. Background

This memorandum is in response to a CSS consult dated July 3, 2012, from the Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) pertaining to NDA204223 for morphine sulfate proposed for the management of pain not responsive to non-narcotic analgesics submitted by Becton Dickinson (BD). In addition to requesting CSS

participation in internal and industry meetings, the consult involves a review of the submitted materials.

B. Conclusions:

Morphine sulfate is a well-documented DEA Schedule II opioid agonist that is proposed in varying concentrations of single-use, pre-filled syringes. Since the proposed dosage strengths in the routes of administration are within the previously approved dose ranges of existing products and the context for use are similar, the exposure risk profile of misuse, abuse, addiction, diversion, and overdose is not likely to differ from the reference listed drugs for intravenous administration of Morphine Sulfate Injection USP by Hospira (NDA 202515) and for intramuscular administration by Meridian Medical (NDA 019999).

C. Recommendations:

1. Sponsor needs to inform the Drug Enforcement Administration of their intent to manufacture this morphine formulation, to request a quota.
2. Sponsor should minimize the risks of addiction, abuse, misuse, overdose, and drug diversion throughout the product life cycle if they are not familiar with the regulatory requirements of formulations containing controlled substances.
3. Detailed narratives on misuse, abuse, addiction, diversion, and overdose should be included in the submission of post-approval periodic safety reports.

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/s/

STEPHEN W SUN
08/16/2012

MICHAEL KLEIN
08/16/2012