CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209949Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 10, 2017
Requesting Office or Division:	Division of Anti- Infective Products (DAIP)
Application Type and Number:	NDA 209949
Product Name and Strength:	Daptomycin for Injection; 350 mg per vial
Applicant/Sponsor Name:	Xellia Pharmaceuticals
Submission Date:	October 6, 2017
OSE RCM #:	2016-2913-1
DMEPA Safety Evaluator:	Sevan Kolejian, Pharm D
DMEPA Team Leader:	Otto L. Townsend, Pharm D

1 PURPOSE OF MEMO

The Division of Anti- Infective Products (DAIP) requested that we review the revised container label and carton labeling for daptomycin for injection (Appendix A) to determine if they are acceptable from a medication error perspective.

1.1 BACKGROUND

We previously reviewed the container label and carton labeling for this product and found them acceptable.[a] We note, Xellia Pharmaceuticals revised the container label and carton labeling by including the National Drug Code (NDC) number and the manufacturer information that was not previously included.

2 CONCLUSION

We find the revised container label and carton labeling acceptable from a medication error perspective and have no further recommendations at this time.

[a] Kolejian, S. Label and Labeling Review for daptomycin for injection (NDA 209949). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUL 17. RCM No.: 2016-2913.

APPENDIX A. LABEL AND LABELING SUBMITTED ON OCTOBER 6, 2017 (AVAILABLE AT

1. Container labels

2. Carton labeling

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

/s/

SEVAN H KOLEJIAN
10/10/2017

OTTO L TOWNSEND
10/10/2017

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 # 209949	NDA Supplement #: S- n/a	Efficacy Supplement Category: n/a
Proprietary Name: **Daptomycin** Established/Proper Name: ***not proposed*** Dosage Form: **Powder for Solution, for Injection** Strengths: **350 mg/vial** Route(s) of Administration: **Intravenous Infusion**		
Applicant**: Xellia Pharmaceuticals ApS** Agent for Applicant (if applicable): **Xellia Pharmaceuticals USA, LLC**		
Date of Application: **December 20, 2016** Date of Receipt: **December 20, 2016** Date clock started after Unacceptable for Filing (UN): n/a		
PDUFA/BsUFA Goal Date: **October 20, 2017**	Action Goal Date (if different): n/a	
Filing Date: **February 18, 2017**	Date of Filing Meeting: **February 9, 2017**	
Chemical Classification (original NDAs only) : **X Type 5- New Formulation or New Manufacturer**		
Proposed indication(s)/Proposed change(s): **Complicated skin and skin structure infections (cSSSI); Staphylococcus aureus bloodstream infections (bacteremia) including those with right-sided infective endocarditis caused by Methicillin-Susceptible and Methicillin-Resistant Isolates**		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) **X 505(b)(2)** ☐ 505(b)(1) ☐ 505(b)(2)	
Review Classification:	**X Standard**	
Part 3 Combination Product? **No** ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	
☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

☐ Direct-to-OTC Other:				
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/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	**X**	☐		
Are the established/proper and applicant names correct in electronic archive? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.***	**X**	☐		No Tradename requested.
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	**X**	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	**X**		
If yes, explain in comment column.				n/a
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	**X**	☐		
User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* X Paid [PD3016502] ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			

If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: X Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** X Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	**X**	☐		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	**X**		
• 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)].**	☐	**X**		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	**X**		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	**X**		No unexpired exclusivity for this daptomycin product in the OB database.

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

• If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify	X	☐		NDA 21-572

one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement **[see 21 CFR 314.50(i)(1)(i)(C) and 314.54]**? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If no,** include template language in the 74-day letter. ***Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]*** ***Note: Pharmaceutical equivalents** are drug products in identical dosage forms and route(s) of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.*				
Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	**X**		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	**X**	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:** An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	**X**	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	**X**	☐	
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)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	**X**	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book***	☐	☐	**X**	

Manager ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) **X** All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	n/a			
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	**X**	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: **X** legible **X** English (or translated into English) **X** pagination **X** navigable hyperlinks (electronic submissions only) **If no**, explain.	**X**	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	**X**	
Forms and Certifications				
***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 (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	**X**	☐		

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

If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].				
Are all establishments and their registration numbers listed on the form/attached to the form?	**X**	☐	☐	
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)?	X	**X**	☐	2/28/17
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)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☐	**X**		Did not conduct clinical studies; biowaiver requested for bioequivalence studies.
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	**X**	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***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].*** ***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…"*	**X**	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	**X**	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?	☐	☐	X	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☐	X		New Strength. 350mg - PREA Not Triggered.
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	X	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	X	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required***[3]	☐	X		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☐	**X**	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☐	**X**	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	**X** Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) **X** Carton labeling **X** Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	**X**	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	**X**	☐		
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? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	**X**	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	X ☐	☐ ☐	☐ X	**Submitted 2/16/17**
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	X	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576 htm

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	**X**	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	**X**	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	**X**	☐	☐	
OTC Labeling	**X Not Applicable**			
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	**X**	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):**	☐	**X**		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):**	☐	**X**		
Any Special Protocol Assessments (SPAs)? **Date(s):**	☐	**X**		

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 9, 2017

BACKGROUND: NDA submitted 12/20/16, as a 505(b)(2) application referencing Cubist Pharmaceuticals, NDA 21-572. The only change in the two products is that this product is a 350 mg vial versus the approved 500 mg vial (Cubist).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Maureen Dillon-Parker	Y
	CPMS/TL:	Same	Y
Cross-Discipline Team Leader (CDTL)	Dorota Matecka, PhD		Y
Division Director/Deputy	Dmitri Iarikov, MD		Y
Office Director/Deputy	n/a		
Clinical	Reviewer:	Alma Davidson, MD	Y
	TL:	Hala Shamsuddin, MD	Y
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Avery Goodwin, PhD	Y
	TL acting:	Tamara Feldblyum, PhD	Y
Clinical Pharmacology	Reviewer:	Sonia Pahwa, PhD	Y
	TL:	Seong Jang, PhD	Y
• Genomics	Reviewer:	n/a	Y
• Pharmacometrics	Reviewer:	n/a	Y
Biostatistics	Reviewer:	Karen Higgins, ScD	Y
	TL:	Karen Higgins, ScD	Y

Nonclinical Pharmacology/Toxicology)	Reviewer:	Terry Miller, PhD	Y
	TL:	Terry Miller, PhD	Y
Statistics (carcinogenicity)	Reviewer:	n/a	
Product Quality (CMC) Review Team:	ATL:	Dorota Matecka, PhD	Y
	RBPM:		
• Drug Substance	Reviewer:	Milton Sloan, PhD	Y
• Drug Product	Reviewer:	Milton Sloan, PhD	Y
• Process	Reviewer:		
• Microbiology	Reviewer:		
• Facility	Reviewer:		
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Sevan Kolejian	
	TL:	Otto Townsend	
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees	Sumathi Nambiar, MD, MPH		Y
	Dmitri Iarikov, MD, PhD		Y
	Katherine Schumann, MS		Y
	Joseph Toerner, MD, MPH		Y

FILING MEETING DISCUSSION:

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

CLINICAL **Comments**: Request for PLLR labeling and Pediatric assessment. Note: Information received from sponsor prior to 74 day letter being issued.	☐ Not Applicable x FILE ☐ REFUSE TO FILE X Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES X NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***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***	☐ YES Date if known: X NO ☐ To be determined ○ Reason: ***the application did not raise significant safety or efficacy issues***
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	X Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

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

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

Annual review of template by OND ADRAs completed: April 2016

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

/s/

MAUREEN P DILLON PARKER
10/03/2017

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

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

Memorandum

Date: August 4, 2017

To: Maureen Dillon Parker
Chief, Project Management Staff
Division of Anti-Infective Products (DAIP)

From: Puja Shah, PharmD, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Consult Response
NDA 209949
DAPTOMYCIN for injection, for intravenous use

As requested in DAIP's consult dated February 17, 2017, OPDP has reviewed the draft Package Insert (PI) and Carton and Container Labeling (CCL) for DAPTOMYCIN for injection, for intravenous use. OPDP's review is based on the substantially complete version of the labeling titled "nda209949.revised.LABELING.June.2017.docx" which was accessed via http://sharepoint.fda.gov/orgs/CDER-OAP-DAIP/Active Documents/nda209949.revised.LABELING.June.2017.docx on August 1, 2017.

Package Insert
OPDP has no comments on the draft PI at this time.

Carton and Container Labeling
OPDP reviewed the following proposed CCL accessed on August 2, 2017, and does not have any comments at this time:

- Draft carton and container labeling accessed via \\cdsesub1\evsprod\nda209949\0004\m1\us\1-14-labeling\1-14-1-draft-labeling\1-14-1-1-draft-carton-container-labels\draft-carton-container-labels.pdf

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Puja Shah at 240-402-5040 or puja.shah@fda.hhs.gov.

42 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/

PUJA J SHAH
08/04/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 17, 2017
Requesting Office or Division:	Division of Anti- Infective Products (DAIP)
Application Type and Number:	NDA 209949
Product Name and Strength:	Daptomycin for Injection; 350 mg per vial
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Xellia Pharmaceuticals
Submission Date:	December 20, 2016, February 16, 2017 and June 23,2017
OSE RCM #:	2016-2913
DMEPA Primary Reviewer:	Sevan Kolejian, Pharm D
DMEPA Team Leader:	Otto L. Townsend, Pharm D

1 REASON FOR REVIEW

The Division of Anti –Infective Products (DAIP) requested that we review the container label, carton labeling, and Prescribing Information (PI) for daptomycin for injection, to determine if they are acceptable from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Xellia Pharmaceuticals submitted a 505(b)(2) New Drug Application for Daptomycin for Injection, 350 mg per vial. The active ingredients, indication, route of administration, and dosage form are the same as reference listed drug, Cubicin, NDA 021572, approved on September 12, 2003. However, the proposed product will have different total amount of drug per vial (350 mg vs. 500 mg) from the reference drug. Thus, the contents of the vial will be reconstituted with 7 ml (instead of 10 mL) of 0.9% sodium chloride injection to yield a final concentration of 50 mg/mL of reconstituted daptomycin for injection. Since the dosing for daptomcyin is always weight based (b) (4)), we do not have any safety concerns with the proposed strength. (b) (4) . To address the difference in the volume of diluent used

[a] (b) (4) .

for reconstitution between the RLD and the proposed product, the Applicant has included the volume (7 ml) on the side panel of both the container label and carton labeling.

We note that the proposed daptomycin for injection and the reference listed drug (RLD), Cubicin, should be reconstituted with 0.9% sodium chloride for injection, and stored in the refrigerator. In contrast, the new formulation, Cubicin RF, which was approved in July 2016, should be reconstituted with sterile water or bacteriostatic water for injection and stored at room temperature. We note that the Sponsor submitted revised label and labeling on June 23, 2017 modeled after the last labeling for the RLD, Cubicin approved on June 9, 2017 which should address potential confusion between Cubicin RF and the proposed product.

4 CONCLUSION & RECOMMENDATIONS

The proposed labels and labeling for Xellia's daptomycin for injection is acceptable from a medication error perspective. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for daptomycin for injection that Xellia Pharmaceuticals submitted on December 20, 2016 , and the listed drug (LD).

Table 2. Relevant Product Information for daptomycin for injection and the Listed Drug		
Product Name	Daptomycin for injection	Cubicin (daptomycin) for injection
Initial Approval Date	N/A	September 12, 2003
Active Ingredient	Daptomycin	
Indication	Treatment of complicated skin and skin structure infections (cSSSI), and *Staphylococcus aureus* bloodstream infections (bacteremia), including those with right-sided infective endocarditis.	
Route of Administration	Intravenous injection	
Dosage Form	Lyophilized powder for reconstitution	
Strength	350 mg/ vial	500 mg/vial
Dose and Frequency	Administered once every 24 hours for 7 to 14 days with a usual dose of 4 mg/kg. The maximum dose will be 6 mg/kg/day.	
How Supplied	350 mg daptomcyin supplied as a sterile pale yellow to light brown lyophilized cake in a single-dose 15 mL vial.	500 mg daptomycin as a sterile, pale yellow to light brown lyophilized powder for reconstitution in a single-dose 10 ml vial.
Storage	Store original packages at **refrigerated temperatures**, 2 to 8°C (36 to 46°F); avoid excessive heat	
Container Closure	15 ml vial	10 ml vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On May 15, 2017, we searched the L:drive and AIMS using the terms, Cubicin and daptomycin to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified thirteen (13) previous reviews[b,c,d,e,f, g,h ,i,j,k,l,m], and we confirmed that our previous recommendations were implemented and considered.

---

[b] Winiarski, A. Label and Labeling Review for daptomycin for injection (NDA 203797). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 FEB 21. OSE RCM No.: 2012-1561.

[c] (b) (4) .

[d] Kolejian S. Daptomycin for Injection 350 mg per vial (NDA 203797) Label Labeling Packaging Review. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 AUG 19. OSE RCM No.: 2016-1435.

[e] (b) (4)

[f] (b) (4)

[g] Kolejian, S. Cubicin NDA 21572 Label Labeling Packaging Review. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 JAN 15. OSE RCM No.: 2014-2635.

[h] Kolejian, S. Cubicin (daptomycin) for injection NDA 21572 Label Labeling Packaging Review MEMO. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 FEB 5. OSE RCM No.: 2014-2635.

[i] Kolejian, S. Label and Labeling Review for Cubicin RF (daptomycin for Injection) (NDA 021572-S052). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 APR 7. OSE RCM No.: 2016-435.

[j] Kolejian, S. Label and Labeling Memorandum for Cubicin RF (daptomycin for Injection) (NDA 021572-S052).Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 MAY 19. OSERCM No.: 2016-435-1

[k] Kolejian, S. Label and Labeling Review for Cubicin RF (daptomycin for Injection) (NDA 021572-S052). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 MAY 13. OSE RCM No.: 2016-435-2.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched FAERS using the criteria below as follow:

On June 2 , 2017 we searched FAERS and retrieved total of 8 FAERS case reports for daptomycin for injection product. We excluded 1 case (n=1) as the case described adverse event anaphylaxis. We individually reviewed the remaining 7 cases, and used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[n]

Criteria Used to Search FAERS	
Initial FDA Receive Dates:	February 1, 2017 to June 1, 2017
Product Name:	Daptomycin
Product Active Ingredient (PAI):	Daptomycin
Event (MedDRA Terms)	Medication errors SMQ (narrow)
Country (Derived):	USA

B.2 Results

Our searches identified total of 7 US FAERS cases. These cases described a medication error associated with incorrect product Storage and/ or product preparation error. We note that in our previous postmarketing review dated March 15, 2017 (RCM No.: 2016-2379[l]), we made recommendations to prevent reconstitution and storage errors associated with different formulations of daptomycin for injection products. Our recommendations were considered and the labels and labeling were revised. We note no new cases were received since revisions were made. The 7 FAERS case numbers are provided in the Line Listing (See E.3)

---

[l] Kolejian, S. Postmarketing Review for Cubicin and Cubicin RF NDA 21572 (TSI 1731). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 MAR 15. OSE RCM No.: 2016-2379.

[m] Kolejian, S. Cubicin and Cubicin RF NDA 21572 Label Labeling Packaging Review MEMO. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 MAR 29. OSE RCM No.: 2017-517.

[n] 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.

E.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

FAERS Case #	Manufacturer Control Number	FDA Initial Received Date	Narrative
13373212	US-009507513-1703USA006835	3/27/2017	This spontaneous report was received from a pharmacist and refers to a 68 year old patient of unspecified gender. The patient□s concurrent conditions, medical history or concomitant medications were not reported. The pharmacist reported that on 14-MAR-2017, a vial of daptomycin (CUBICIN) (indication, dose and frequency were not reported) (lot 929621, expiration date in May 20419) was **reconstituted with 10mL of Sterile Water for Injection (manufacturer: Hospira)**. The vial was not been placed into a diluent at the time of the call. The pharmacist stated that the daptomycin (CUBICIN) might be used for the patient. No adverse effects were reported. Additional information has been requested.
13398115	US-009507513-1703USA006870	4/3/2017	Information was received on 14-MAR-2017 from a pharmacist. The pharmacist reported that an unspecified infusion center had been storing daptomycin (CUBICIN) (lot and expiration unspecified) **after reconstitution for 10 days in the refrigerator** and the medication was administered to an unspecified number of patients on unspecified dates (dose, lot, expiration, frequency and indication not reported). No medical history, concomitant medications or any patient identifiers were reported for these patients. No adverse effects were reported. No other information was provided. All telephone attempts to obtain follow-up information have been unsuccessful. Additional information has been requested.
13416775	US-009507513-1703USA009330	4/7/2017	This spontaneous report was received from a pharmacist and refers to multiple unspecified patients of unknown age and gender. There was no information about the patients' pertinent medical history, drug reactions or allergies and concomitant medications provided. On unknown dates, the patients were treated with daptomycin **(CUBICIN) RF** (dose, route, lot # and expiration date and indication were not provided) that were inadvertently stored **"in the refrigerator"** before reconstitution and that were inadvertently reconstituted with saline which is outside the prescribing information. No adverse effects reported. No information regarding the temperature and time frame for daptomycin (CUBICIN) RF excursion were provided. It was not reported if previous temperature excursion occurred. Data logger information was not provided. A product quality complaint (PQC) was not involved. Follow up information has been received on 25-APR-2017 that all telephone attempts to obtain follow-up information had been unsuccessful. Additional information has been requested.

13492233	US-009507513-1704USA007134	4/27/2017	Information was received on 14-APR-2017 from a pharmacist regarding multiple unspecified patients. Medical history, concurrent conditions and concomitant medications were not reported. On unspecified dates multiple patients received daptomycin (CUBICIN VIAL 500mg)(lot # 930057, expiration date 30-SEP-2019) (indication not specified), **reconstituted in BD syringes with normal saline** at the concentration of 50mg/ml and **stored at refrigerated temperatures** (36 degrees Fahrenheit to 46 degrees Fahrenheit) for longer than 48 hours. No adverse effects reported. No additional information was provided. The action taken was not applicable and the outcome was unknown. Lot number 930057, expiration date 30-SEP-2019 has been confirmation to be a valid lot number for daptomycin (CUBICIN). Follow up information has been received on 08-MAY-2017 from a pharmacist. The pharmacist reported that multiple lots of daptomycin (CUBICIN) were stored in this manner. She stated that multiple patients had received these improperly stored products and no adverse events were noted. She clarified that this facility has continued to practice this improper store currently. Additional information has been requested.
13276147	US-009507513-1702USA011539	2/28/2017	This spontaneous report was received from a registered pharmacist and refers to a patient of unknown age and gender. The patient's pertinent medical history, drug reactions, allergies and concomitant medications were not reported. The pharmacist reported that on an unknown date, daptomycin **(CUBICIN RF)** (dose, indication, lot# and expiration date were not reported) was reconstituted with sterile water for Injection and transferred into a infusion bag with normal saline using a 18 gauge needle **(Wrong solution used in drug reconstitution**). No adverse effects were reported. Product quality complaint (PQC) was not involved. Additional information has been requested.
13367818	US-009507513-1703USA005229	3/24/2017	This spontaneous report was received from a pharmacist technician, referring to multiple unknown patients of unknown age and gender. Information regarding the patients' pertinent medical history, concurrent conditions, known allergies and concomitant medications was not provided. On unknown multiple dates, the patients were administered with improperly stored with daptomycin (CUBICIN RF) (strength, dose, frequency, route, lot number and expiration date were not provided). The primary reporter stated that, the wholesaler/distributer stored daptomycin (**CUBICIN RF**) in the refrigerator at unknown temperatures, for unknown time frames. It was not reported if daptomycin (CUBICIN RF) was part of previous temperature excursions. Possible adverse effects were unknown. No product quality issue was involved. Additional information is not expected as correspondence contact was not provided.
13416192	US-009507513-1704USA002539	4/7/2017	Information has been received from **TEVA** (MCN# TGN17-007902) on 05-APR-2017. This spontaneous report as received from a consumer (also reported as pharmacist) refers to a patient of unknown age and gender. On an unknown date, the patient started therapy with daptomycin (manufacturer unknown) injection, strength 500 mg/vial, lot number reported as 929117 (dosing details, route and indication unknown). The reporter informed that, on 05-APR-2017, while using daptomycin (manufacturer unknown) injection, the **vial was diluted with sterile water** and dispensed to the nursing floor but has not been administered at this time (product preparation error). As of 11-APR-2017, upon internal clarification, it was confirmed that the

			primary reporter was a pharmacist. Lot number 929117 has been verified to be a valid lot number for daptomycin. Additional information has been requested.

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[o] along with postmarket medication error data, we reviewed the following daptomycin for injection labels and labeling submitted by Xellia Pharmaceuticals on June 23, 2016.

- Container label
- Carton labeling

G.2 Label and Labeling Images (available at: Application 209949 - Sequence 0004 - draft-carton-container-labels)

1. Container label

2. Carton labeling

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

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

/s/

SEVAN H KOLEJIAN
07/17/2017

OTTO L TOWNSEND
07/17/2017