

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205917Orig1s000

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 31, 2014
Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number: NDA 205917
Product Name and Strength: Paricalcitol Injection, 2 mcg/mL, 5 mcg/mL, and 5 mcg/2 mL
Submission Date: October 8, 2014 and October 30, 2014
Applicant/Sponsor Name: Hikma Pharmaceuticals
OSE RCM #: 2013-2112-1
DMEPA Primary Reviewer: Tingting Gao, PharmD
DMEPA Team Leader: Yelena Maslov, PharmD

1 PURPOSE OF MEMO

Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised container labels (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSIONS

While the revised container labels for 2 mcg/mL and 5 mcg/mL strengths are acceptable from a medication error perspective, we have a safety concern regarding to the revised container label for the 10 mcg/2 mL strength. We note that the concentration per milliliter is presented as (b) (4) (b) (4) instead of '5 mcg/mL', which is inconsistent with USP General Chapter <1>, which states "Strength per single mL should be expressed as mg/mL, (b) (4)".

¹ Gao T. Label and Labeling Review for Paricalcitol (NDA 205917). 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); 2014 MAY 28. 13 p. OSE RCM No.: 2013-2112.

2.1 RECOMMENDATION TO HIKMA PHARMACEUTICALS

- A. Container label for 10 mcg/2 mL
 - a. Revise the (b) (4) concentration statement to '5 mcg/mL' in accordance with USP General Chapter <1>.

APPENDIX A. LABEL AND LABELING SUBMITTED ON OCTOBER 8, 2014 AND OCTOBER 30, 2014

(b) (4)



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/s/

TINGTING N GAO
10/31/2014

YELENA L MASLOV
11/03/2014



Memorandum

DATE: AUGUST 29, 2014

FROM: Michelle Luo, Ph.D, Biologist
Renal Devices Branch/DRGUD
ODE/CDRH

TO: Williams Lubas, Medical Officer
CDER/OND/DMEP

Pamela Lucarelli
Chief, Project Management Staff
CDER/OND/DMEP

Keith Marin, RN, MS, MBA
Combination Product Team Lead
General Hospital Devices Branch
DAGRID/ODE/CDRH

THROUGH: Carolyn Neuland, Ph.D, Branch Chief
Renal Devices Branch
DRGUD/ODE/CDRH

SUBJECT: NDA 205917- Consult
Paricalcitol- An injectable drug for the hemodialysis patient

BACKGROUND

On July 07, 2014, I was requested by Keith Marin, Combination Product Team Leader in DAGRID/ODE/CDRH, regarding an inter-center request from CDER, to provide a consult on an NDA application for the proposed drug product, Paricalcitol Injection, 2mcg/ml and 5 mcg/ml from Exela, Inc.

The proposed drug product, Paricalcitol Injection, is intended for the prevention and treatment of secondary hyperparathyroidism associated with stage 5 chronic kidney disease (CKD). In this NDA application, the sponsor has listed Zemplar (Paricalcitol), a drug from Abbott, as the approved reference drug. The chemical composition of Zemplar is 19-nor-1,25-(OH)₂-vitamin D₂ or 19-nor-1,25-dihydroxyvitamin D₂. This medication is an analog of vitamin D₂ (Ergocalciferol) that acts as an agonist for the vitamin D receptor.

The sponsor states that the proposed drug product Paricalcitol has the same active ingredient, dosage form, strength, route of administration, and conditions of use as Zemplar Injection. However, the proposed drug product differs from Abbott’s drug product with respect to the solubilizers used to dissolve the active ingredient. Exela’s formulation contains 35% v/v alcohol, whereas the concentration of alcohol is 20% v/v in Abbott’s Zemplar (paricalcitol) Injection.

On September 27, 2011, CDER sent an Information Request asking the sponsor to address the safety of using a 35% alcohol formulation and the potential impact of this formulation on infusion tubing, related materials and on a patient’s hemodialysis access (eg, arteriovenous fistula, or AVF). The sponsor sent the responses on June 07, 2014. In this consult, CDER has requested the input from CDRH on the sponsor’s response.

DISCUSSION

As shown in the table below provided in the sponsor’s response, the proposed (Exela) Paricalcitol Injection’s formulation contains 35% v/v alcohol, 7% v/v sorbitol solution whereas the Zemplar Injection (Abbott) contains a concentration of 20% v/v alcohol and 30% v/v propylene glycol.

1.3 COMPARISON OF EXELA'S PARICALCITOL INJECTION DRUG PRODUCT WITH ABBOTT LABORATORIES ZEMPLAR® (PARICALCITOL) INJECTION.

Ingredients	Exela’s Formulation	Abbott Laboratories Formulation¹
Paricalcitol, USP	2 µg/mL or 5 µg/mL	2 µg/mL or 5 µg/mL
Alcohol, 190 proof, USP	35% v/v	20% v/v
Propylene Glycol, USP		30% v/v
Sorbitol Solution, 70%, USP	7% v/v	
Water for Injection, USP	q.s.	q.s.

In an email communication with CDER, Dr. William Lubas indicated that the proposed labeling for the administration of the drug is as the follows:

[REDACTED] (b) (4)

Based on this proposed labeling, the highest recommended initial dose of 7 mcg would require 1.4 mL of the 5mcg/mL solution to be administered. Assuming that 2 dose increases of 2-4 mcg may occur, the highest dose to be administered would be 15 mcg. A dose of 15 mcg would

require 3 mL of the 5 mcg/mL formulation to be administered. Paricalcitol is administered via the dialysis tubing to the patient, via dialysis access (e.g, AVF).

In their response, the sponsor has provided JMS hemodialysis blood tubing sets as an example not raising any biocompatibility concerns. Under current CDRH regulations, blood tubing sets are class II medical devices, regulated under 21 CFR 876.5820. The materials used in the JMS tubing sets are mainly polyvinylchloride (PVC), polyethylene (PE), polypropylene (PP), acrylonitrile butadiene styrene (ABS), and polycarbonate (PC). These materials are commonly used in the medical devices and their safety has been verified for patients receiving hemodialysis. However, since the sponsor did not test other hemodialysis blood tubing sets, the drug labeling should indicate that the safety of the drug with other tubing sets cannot be confirmed.

I have discussed the issue of the safety of the alcohol content in the proposed drug with Dr. Xin Fu, a former toxicologist in ULDB/DRGUD/ODE, now in the Center for Tobacco Products (CTP). She agreed that the potential impact of the proposed formulation on the leachable effects on the materials of the infusion tubing sets would be minimal because of the very short period of time that the tubing materials are exposed to the alcohol. Furthermore, the proposed labeling states that the drug product should not be injected directly into the vein. Therefore, the safety concerns of the high alcohol concentration on the patients should be properly mitigated.

The concerns of the how much of 35% alcohol will be diluted in the dialysis machine were further discussed with Dr. William Lubas. In the sponsor's response, they have provided the table below indicating the degree that Paricalcitol, with an alcohol concentration of 40% in the doses described above, would be diluted by a blood flow rate of 300 mL/minute.

Table 1. Dilution of Alcohol in Paricalcitol Formulation Following Administration During Dialysis

Alcohol Concentration	Time (seconds) after Administration of Specified Dose Volume	
	7 mcg (1.4 mL)	15 mcg (3 mL)
40% (initial)	0.00	0.00
20%	0.28	0.60
10%	0.56	1.20
5%	1.12	2.40

The sponsor concludes from the table that with the rapid dilution of the administered volume injection into a dialysis circuit, a maximum dose (15 mcg, 3 ml) of Paricalcitol, with an alcohol concentration of 40%, would be diluted to an alcohol concentration below that observed for other drugs administered intravenously with 5% alcohol content. However, because in dialysis patients the drugs are usually injected into the downstream side of the dialyzer where the blood flow rate is variable, and is unlikely to be a blood flow of 300 mL/minute, the final concentration of the 35% alcohol to be diluted in the tubing set is unknown. The data presented in this submission did not address the variable blood flow rates in the tubing sets on the downstream side of the dialyzers.

I have discussed this concern with Dr. Frank Hurst, M.D and Dr. Douglas Silverstein, M.D who are Nephrologists in RNDB/ODE/CDRH. We recommend that CDER consult with an expert in fluid dynamics or request the sponsor or the drug manufacture to conduct a mock circuit or

modeling study to figure out what happens to the drug after it is injected in the blood tubing downstream of the dialyzer. It is recommended that the test be conducted to address the variable blood flow rate in the tubing sets on the downstream sides of the dialyzers.

Digital Signature Concurrence Table	
Reviewer Sign-Off	
Branch Chief Sign-Off	

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/s/

MEGHNA M JAIRATH
09/10/2014

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: May 28, 2014
Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number: NDA 205917
Product Name and Strength: Paricalcitol Injection, 2 mcg/mL, 5 mcg/mL, and 5 mcg/2 mL
Product Type: Single Ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: Exela Pharma Sciences, LLC
Submission Date: June 7, 2013
OSE RCM #: 2013-2112
DMEPA Primary Reviewer: Tingting Gao, PharmD
DMEPA Team Leader: Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container label, carton labeling, and prescribing information for Paricalcitol Injection for areas of vulnerability that could lead to medication errors. This is a 505(b)(2) Application and the listed drug is Zemplar (paricalcitol) Injection, NDA 20819, approved on April 17, 1998.

The Division of Metabolism and Endocrinology Products (DMEP) requested that we review the submitted Paricalcitol labels and labeling for areas of vulnerability that may lead to medication errors.

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
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study (if applicable)	D – N/A
ISMP Newsletters	E
Other (if applicable)	F – N/A
Container Label, Carton Labeling, and Instructions for Use or Medication Guide (if applicable)	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our search of the FAERS database identified seven cases of wrong route of administration that is relevant to our label and labeling review. We evaluated the currently approved Zemplar® Prescribing Information (PI) labeling and identified that the route of administration is not explicitly stated in the Dosage and Administration section. Additionally, we noted that the route of administration is also not explicitly stated in the Dosage and Administration section of the proposed PI labeling for Paricalcitol. As a result, we recommend adding the correct route of administration in the Dosage and Administration section of the proposed PI labeling.

Additionally, we identified the following additional areas of vulnerability to error in the prescribing information labeling:

- The statement of strength is presented as [REDACTED] (b) (4) in the Dosage Forms and Strengths section of the insert labeling. This strength presentation is not in accordance with the recommendations provided in United States Pharmacopeia (USP) General Chapter <1> Injections and FDA Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.
- The container labels indicate that the 2 mcg/mL, 5 mcg/mL, and 5 mcg/2 mL vials are single-dose vials. This information is not included in the How Supplied/Storage and Handling section in the Prescribing Information labeling. Lack of this important information in the PI may make it more difficult for pharmacy purchasing agents to determine the number of vials to order during pharmacy procurement process.

We also identified the following areas of vulnerability to error in the container label:

- The statement “Rx ONLY” on the container label principal display panel competes for prominence with other important information as such established name and strength.
- For the 10 mcg/2 mL vial, the total drug content is presented only as total strength per total amount of milliliters. The strength per milliliter is not listed on the vial label.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed container label and prescribing information insert can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product to mitigate any confusion. We provide the following recommendations be implemented prior to approval of this NDA:

4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA provides the following comments for consideration by the review Division prior to the approval of this NDA:

- A. Dosage and Administration section in Highlights of Prescribing Information and Full Prescribing Information
 - a. The route of administration is not explicitly stated. Although we recognize the Applicant is following the innovator’s insert labeling, we recommend revising [REDACTED] (b) (4) to read “The

recommended initial dose of Paricalcitol is 0.04 mcg/kg to 0.1 mcg/kg (2.8 - 7 mcg) administered *intravenously* as a bolus dose no more frequently . . .”

Additionally, we recommend the inclusion of the statement, ‘For Intravenous Use Only’ after the heading ‘2 DOSAGE AND ADMINISTRATION’ to further increase the reader’s awareness of the proper route of administration for this drug product.

B. Dosage Forms and Strengths section in Full Prescribing Information

- a. Delete the (b) (4) from the statement of strength presentation so that this information is not misinterpreted. For example, (b) (4) should be revised to read “2 mcg/mL” in accordance with the United States Pharmacopeia (USP) General Chapter <1> Injections and FDA Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.

C. How Supplied/Storage and Handling section in Full Prescribing Information

- a. Add a 5th column to the right of the “Total Content” column in the table to indicate the vial type (e.g. single-use vial, multi-use vial).
- b. Revise (b) (4) to “NDC Number” as NDC Number is the terminology that healthcare professionals are familiar with and is often used as an additional verification for drug product identification.

4.2 RECOMMENDATIONS FOR THE APPLICANT

A. Container label

- a. Move the statement “Rx ONLY” away from the middle of the principal display panel as this information competes for prominence with the established name and strength on the principal display panel.
- b. As currently presented, the strength presentation for the 10 mcg/2 mL vial only lists the total quantity per total volume. Add the concentration per milliliter (5 mcg/mL) below the strength “10 mcg/2 mL” as demonstrated by the example below:

10 mcg/2 mL
(5 mcg/mL)

We recommend this to ensure that the labels and labeling conform with the United States Pharmacopeia (USP) General Chapter <1> Injections. Revise the statement of strength to increase the prominence of the statement of total drug content in terms of total strength per total amount of milliliters on the principal display panel followed in close proximity by strength per milliliter enclosed by parentheses.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Paricalcitol that Exela Pharma Sciences, LLC submitted on June 7, 2013 and April 7, 2014, and the listed drug.

Table 2. Relevant Product Information for Paricalcitol and the Listed Drug		
Product Name	Paricalcitol	Zemplar (Listed Drug)
Active Ingredient	Paricalcitol	
Indication	Prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5.	
Route of Administration	Intravenous	
Dosage Form	Solution for Injection	
Strength	2 mcg per mL 5 mcg per mL 10 mcg per 2 mL (5 mcg per mL)	
Dose and Frequency	<p>Initial: 0.04 mcg/kg to 0.1 mcg/kg (2.8 – 7 mcg) administered as a bolus dose no more frequently (b) (4) at any time during dialysis.</p> <p>Adjust dose: Dose may be increased by 2 to 4 mcg and 2- to 4- week intervals.</p>	
How Supplied	2 mcg per mL 5 mcg per mL 10 mcg per 2 mL	<p>Single-dose vial: 2 mcg per mL 5 mcg per mL 10 mcg per 2 mL</p> <p>Multi-dose vial: 10 mcg per 2 mL</p>
Storage	25°C (77°C). Excursions permitted between 15°C - 30°C (59°F - 86°F).	
Container Closure	1 mL and 2 mL flip-top vials	

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on April 10, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling.

Table 3: FAERS Search Strategy	
Date of Search	April 10, 2014
Drug Names	Paricalcitol [active ingredient]
MedDRA Search Strategy	Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Quality Issues (NEC)[HLT]

B.2 Results

Our search identified 42 cases, of which 10 described errors that should be evaluated further to identify whether they are possibly associated with the current labels and labeling for Paricalcitol. We excluded 32 cases because they described Zemplar capsules (n = 10), look-alike labeling between Zemplar and another product that is made by different manufacturer (n = 10), adverse drug reaction not associated with a medication error (n = 4), dose omission due to patient missed a dose or stopped taking the drug (n = 3), intentional overdose (n = 1), no lot or expiration date on drug samples (n = 1), medication error associated with paricalcitol as a concomitant medication (n=1), intentional underdose by patient due to financial reasons (n = 1), and extravasation (n = 1).

Following exclusion, 10 cases remained for further analysis. One case was counted twice as it concerned wrong drug and wrong route of administration and, therefore, was assessed as two separate medication error cases. The cases are categorized as follows:

Wrong route (n = 7)

Seven cases involved the administration of Zemplar by the wrong route. Six patients received Zemplar subcutaneously and one patient received the drug intramuscularly. Four of the seven patients who received the drug subcutaneously experienced injection site reactions (stinging, redness, tissue necrosis) and hypocalcemia, whereas the outcomes for the other three patients were not provided. The patient who received the drug intramuscularly complained that the injection hurt and the pain resolved after the medication was given.

Contributing factors were not identified in five of the seven reports. In one case where the patient received Zemplar intramuscularly, the error may have occurred due to patient getting a hepatitis B vaccine intramuscularly prior to the Zemplar injection. In another case where the patient received Zemplar subcutaneously, we attributed the wrong route error to the fact that

patient was supposed to receive Epogen subcutaneously but received Zemiplar subcutaneously in error.

Additionally, we evaluated the currently approved Zemiplar® Prescribing Information (PI) labeling and identified that the route of administration is not explicitly stated in the Dosage and Administration section. Additionally, we noted that the route of administration is also not explicitly stated in the Dosage and Administration section of the proposed PI labeling for Paricalcitol. As a result, we recommend adding the correct route of administration in the Dosage and Administration section of the proposed PI labeling.

Wrong drug (n = 1)

This case describes a patient who received Zemiplar (2 mcg/mL, 1 mL vial) instead of Epogen while on dialysis at home. The reporter stated that the patient's mother confused the vial of Zemiplar with that of Epogen and intended to inject the patient with Epogen via subcutaneous route. Patient experienced hypocalcemia and Zemiplar was discontinued. Therefore, this error does not appear to be associated with the label and labeling of the product.

Overdose (n = 3)

One case reported an overdose resulting in hypercalcemia because patient's Zemiplar dose was not adjusted despite an increase in calcium and parathyroid hormone (PTH) levels. No contributing factors were identified. As a result, we are unable to analyze this further.

One case reported an overdose where the patient received 23 mcg instead of 3 mcg. Patient experienced cramping all over during the patient's dialysis that was resolved when the patient was given saline. This error occurred because the person entering the dose accidentally wrote 23 mcg instead of 3 mcg. Therefore, this error does not appear to be associated with the label and labeling of the product.

One case reported an overdose where the patient received 20 mcg/4 mL instead of 4 mcg/0.8 mL. No patient outcome was reported for this error. This error might have occurred due to confusion between 4 mcg and 4 mL. However, this error does not appear to be associated with the label and labeling of the proposed product.

B.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 #	Case Version #	Manufacturer Control #
3701872	1	None listed
3708471	1	None listed
3802757	1	None listed

3944686	1	None listed
6474298	1	None listed
6540808	1	US-ABBOTT-08P-163-0434913-00
6571228	1	None listed
6572520	1	None listed
6605665	1	SE-ABBOTT-08P-150-0444481-00
6639997	1	US-ABBOTT-07P-163-0374203-00
6698019	1	None listed
6998766	1	US-ABBOTT-09P-163-0561156-00
7905181	1	US-ABBOTT-11P-163-0704486-00
7905183	1	US-ABBOTT-10P-163-0659344-00
7905187	1	US-ABBOTT-11P-163-0704868-00
7905193	1	US-ABBOTT-10P-163-0647838-00
8011161	1	US-ABBOTT-07P-163-0376072-00
9236063	1	US-ABBOTT-12P-163-0928566-00
9490451	1	None listed
9890907	1	None listed

B.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. Adverse events and medication errors are coded 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 C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Drive on April 14, 2014 using the terms, Paricalcitol to identify reviews previously performed by DMEPA.

C.2 Results

We identified the following review:

OSE #2011-1771, Label and Labeling Review for Paricalcitol Injection, NDA 201657, dated December 6, 2011.

APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on April 14, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletters Searched	Acute Care and Community
ISMP Newsletter Search Strategy	Match Exact word or phrase
Search Terms	Paricalcitol

E.2 Results

Our search identified one article described an error associated with a mixup of a vial of Zemplar (paricalcitol) 5 mcg/mL and a vial of fosphenytoin 100 mg PE/2 mL due to its look-alike packaging. Both vials have a green flip-top cap with a white label that contains the drug name in green font color.¹

This case is not relevant to this review because the drug name on the proposed vial labels is in a black font color.

¹ Institute for Safe Medication Practices. Safety briefs: Look-alike vials. ISMP Med Saf Alert Acute Care. 2008;13(4):1.

APPENDIX G. CONTAINER LABEL, CARTON LABELING, INSTRUCTIONS FOR USE, MEDICATION GUIDE

G.1 List of Label and Labeling Reviewed

We reviewed the following Paricalcitol labels and labeling submitted by Exela Pharma Sciences, LLC on June 7, 2013, September 25, 2013, April 7, 2014, and May 15, 2014.

- Container label
- Prescribing Information Insert (not included)

G.2 Label and Labeling Images

Container Label





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/s/

TINGTING N GAO
05/28/2014

YELENA L MASLOV
05/28/2014

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 # 205917 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: Paricalcitol injection Dosage Form: intravenous solution Strengths: 2 mcg/mL (1 mL vials), 5 mcg/mL (1 mL and 2 ml vials)		
Applicant: Hikma Pharmaceuticals Co. Ltd Agent for Applicant (if applicable): Exela Pharma Sciences LLC		
Date of Application: June 7, 2013 Date of Receipt: June 10, 2013 Date clock started after UN:		
PDUFA Goal Date: April 10, 2014	Action Goal Date (if different):	
Filing Date: August 9, 2013	Date of Filing Meeting: July 29, 2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication(s)/Proposed change(s): Paricalcitol is indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" 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>	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
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 checked="" type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <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 Designation <input type="checkbox"/> Breakthrough Therapy Designation <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 (<i>if OTC product</i>): n/a				
List referenced IND Number(s): IND (b) (4)				
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>	x			
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>	x			
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>	x			
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>		x		
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?		x		

<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 any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1488 1349 1623"> <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 may block the approval but 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</i></p>		<p>×</p>																		

<p>Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</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? (NDAs/NDA efficacy supplements only)</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 (NDAs only)?</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 checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input checked="" 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>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>		×		It is in non-CTD format. No waiver granted.
<p>Index: Does the submission contain an accurate comprehensive index?</p>	×			yes
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2</p>	x			

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

(BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input 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 #			×	
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?	×			
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)?		×		They sent patent certification information on Paragraph II, III and IV.
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>		×		No clinical study done.
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	×			

<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>				
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, both 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>		×		Not signed by applicant only agent.
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:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</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,</i></p>		×		Confirmed by clinical team in email dated 8.13.13.

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

<i>new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?				
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? <i>If no, request in 74-day letter</i>				
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)? <i>If no, request in 74-day letter</i>				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		×		
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		×		
Prescription Labeling	<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 type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input 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		×		Sponsor submitted this on August 23,

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

format?				2013 via email and to the NDA.
<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 WORD 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 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?				
<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)		×		

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

<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>		×		Sponsor submitted a Pre-IND meeting request under pre-IND (b) (4) which was denied. The sponsor then submitted the IND, after the 30 day safety review they were allowed to proceed with their 2 BE studies.
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 29, 2013

BLA/NDA/Supp #: NDA 205917

PROPRIETARY NAME: None submitted

ESTABLISHED/PROPER NAME: Paricalcitol injection

DOSAGE FORM/STRENGTH : Intravenous solution in 2 mcg/mL (1 mL vials) or 5 mcg/mL (1 mL and 2 ml vials)

APPLICANT: Hikma Pharmaceuticals Co. Ltd

Authorized US agent: Exela Pharma Sciences, LLC.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): For the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5.

BACKGROUND: Sponsor submitted this New 505 (b)(2) NDA 205917 application for paricalcitol injection for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5. Sponsor had previously withdrawn this application under NDA (b)(4) since we told them we would Refuse-To-File their application.

Sponsor is proposing their drug product has the same active ingredient, dosage form, strength, route of administration, and conditions of use as the listed product Zemplar (paricalcitol) Injection. However, their drug product differs from Zemplar with respect to the solubilizers used to dissolve the active ingredient.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Meghna. M Jairath	Y
	CPMS/TL:	Mehreen H. Hai (acting)	
Cross-Discipline Team Leader (CDTL)	Mary Parks Division Director		Y
Clinical	Reviewer:	William (Bill) Lubas	Y

	TL:	Dragos Roman	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:	Zhihong Li	Y
	TL:	Immo Zadenzensky	Y
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Parvaneh Espandiari	Y
	TL:	Karen Davis-Bruno	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Muthukumar Ramaswamy	N
	TL:	Suong Tran Danae Christodoulou	Y N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Robert Mello	Y
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	<u>Biopharmaceutics</u> Banu Zolnik Tapash Gosh <u>Safety</u> Amy Egan		Y Y Y
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES × <input type="checkbox"/> NO × <input type="checkbox"/> YES <input type="checkbox"/> NO Sponsor did a bridging nonclinical 28-day repeat-dose toxicology GLP study was performed using a head-to-head comparison between Exela’s Paricalcitol Injection and listed drug Zemplar (paricalcitol) Injection.
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	× <input 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>	<input type="checkbox"/> Not Applicable × <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<p>Comments: none</p>	<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 study done.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></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> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <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"> 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 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: none</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 type="checkbox"/> YES <input type="checkbox"/> NO

<p>BIOSTATISTICS</p> <p>Comments:</p>	<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>
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments: none</p>	<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>
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<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>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: yes</p>	<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>
<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: CMC review dated 7/26/13 in DARRTS located on page 8.</p>	<p> <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO </p>
<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: none</p>	<p> <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO </p>

<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: CMC review dated 7/26/13 located on pages 6 to 8.</p>	<p><input type="checkbox"/> Not Applicable</p> <p>× <input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p>× <input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments: none</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p>× <input type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Meghna M. Jairath, Pharm.D.</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
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): <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"/>	<p>If priority review:</p> <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"/>	<p>Send review issues/no review issues by day 74</p>
<input type="checkbox"/>	<p>Conduct a PLR format labeling review and include labeling issues in the 74-day letter</p>
<input type="checkbox"/>	<p>Update the PDUFA V DARRTS page (for NME NDAs in the Program)</p>
<input type="checkbox"/>	<p>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]</p>
<input type="checkbox"/>	<p>Other</p>

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/

MEGHNA M JAIRATH
09/09/2013