CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208010Orig1s000

CHEMISTRY REVIEW(S)

Recommendation:
NDA: Approval

NDA 208010
Review 1

Drug Name/Dosage Form	Calcifediol (b)(4) capsules
Strength	30mcg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	OPKO Ireland Global Holding Ltd.
US agent, if applicable	Jane Hsaio, Ph.D. MBA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SN 0000	05/29/2015	All

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
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Laboratory (OTR)	N/A	
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Environmental Assessment (EA)	N/A	

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b)(4)	Type II	(b)(4)	(b)(4)	Adequate	12/22/2015	DMF will be updated with amendment in next Annual Report.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

2. CONSULTS:

None

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The NDA is recommended for approval from manufacturing process and controls perspective at the proposed (b)(4) batch size.

Tarun Mehta, Chemist
01/07/2016

Secondary Review Comments and Concurrence:
Concur with reviewer assessment and conclusion of the manufacturing process and controls proposed in this NDA and also the supporting DMF; the NDA is recommended for approval. Ubrani V. Venkataram, Acting Branch Chief, Branch 6/DPA II/OPF, 08-Jan-2016

ASSESSMENT OF MICROBIOLOGY

10. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:

The proposed specification for the drug product includes microbiological testing consistent with nonsterile, oral capsule dosage forms. The testing is above and beyond the recommendations of USP <1111> for nonsterile dosage forms, and consistent with ICH Q6A for capsule drug products. Total aerobic microbial count and total yeast and molds are testing to not more than 1000 and 100 cfu/g. The capsule shell is from (b)(4) origin, however as additional safety, testing is conducted for Salmonella, Pseudomonas, and Staphylococcus aureus, in addition to USP recommended Escherichia coli.

Microbial Limits Testing			
Total aerobic microbial	279/USP <61>, <62>	Microbial enumeration test	≤1000 cfu/g
Total yeast and mold	285/USP <61>, <62>		≤100 cfu/g
E. coli	287/USP <61>, <62>	Test for specified microorganism	Absent in 1g
Salmonella sp.	286/USP <61>, <62>		Absent in 10 g
S. aureus	288/USP <61>, <62>		Absent in 1 g
P. aeruginosa	289/USP <61>, <62>		Absent in 1 g

Reviewer's Assessment: Adequate

2.3.P.7 Container/Closure System

11. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response:

The container closure system is a white opaque high-density polyethylene (HDPE), 30 cc wide-mouth, round bottle with a (b)(4) white opaque (b)(4) screw cap.The materials provide protection from (b)(4) (b)(4)

Reviewer's Assessment: Adequate

The drug product is solid oral dosage form packed in HPDE bottle.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

12. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response:

Rayaldee capsules do not contain any excipients of human or animal origin.

Reviewer's Assessment: NA

13. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response:

Rayaldee capsules do not contain any excipients of human or animal origin.

Reviewer's Assessment: NA

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Adequate

The drug product release specification includes adequate microbial control testing in accordance with USP and ICH guideline.

Secondary Review Comments and Concurrence:

Concur with reviewer evaluation and recommendation. Ubrani V. Venkataram, Acting Branch Chief, Branch 6/DPA II/OPF, 08-Jan-2016

I. List of Deficiencies to Be Communicated

Note: These deficiencies were sent in an IR letter and the applicant has responded to all the deficiencies adequately.

Process

Provide the following information in support of your NDA.

1. A table comparing the pilot scale batch record and commercial scale batch record in the table include batch size and the drug product composition, unit operation, manufacturing step and/or page number; justify differences between pilot scale and commercial scale manufacturing.

2. For each manufacturing unit operation, provide a detailed description of the types of equipment used, such as vessel, mixer, homogenizer and hopper, used to produce pilot batches and proposed for commercial scale batches; provide diagrams of the equipment. Provide the process controls with justification and supporting data.

3. A table comparing critical process parameters and in-process tests, with acceptable limits/ranges, for pilot and proposed commercial scale batches. Note

that Table 4 of NDA sec. 2.3.P.3 is not sufficient. Provide a justification, if applicable, for any change between the pilot scale and commercial scale batches.

4. Information on how you validated [redacted] Discuss with supporting data. Include it in the manufacturing process as an in-process parameter.

5. Data from enhanced testing of Lot 1237682 submitted in NDA section 3.2.P.2.3 under Table 16 and [redacted] indicates that the samples [redacted] do not show adequate and consistent sampling and test. Provide the data and process parameters that were used to monitor [redacted] process of registration batches. Indicate what the proposed parameters will be for the commercial scale process.

6. [redacted]

7. Define the hold time for each unit operation based on adequate supporting data.

8. With regard to your EBR for product [redacted] Lot 1381098:

[redacted]

(b)(4)

IR for DMF (b)(4)

1. (b)(4)
2.
3.
4.
5.

(b)(4)

6. [redacted]

7. [redacted]

8. [redacted]

9. [redacted]

10. Please update your DMF with all the changes.

ASSESSMENT OF THE BIOPHARMACEUTICS

1. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

Raydaldee (calcifediol) [redacted] capsule is indicated for the [redacted] treatment of secondary hyperparathyroidism (SHPT) in [redacted] with stage 3 or 4 chronic kidney disease (CKD) and [redacted] Oral immediate release formulation of calcifediol was approved in the United States (US) in 1980 as Calderol® for the treatment for metabolic bone disease in dialysis patients. It was withdrawn from the market in 2002 for commercial reasons not associated with safety or efficacy.

The formulation for Rayaldee capsules is reportedly a stable [redacted] soft capsule [redacted] that contains 30 µg of calcifediol and excipients. It is intended to provide a slow release of calcifediol characterized by a gradual increase to attend a lower maximum concentration of serum calcifediol (25-hydroxyvitamin D3) (Cmax) with a longer time to achieve Cmax (Tmax) compared to the immediate-release formulation.

As stated by the Applicant, the Phase 2 and 3 clinical studies have demonstrated that gradual elevation of serum 25-hydroxyvitamin D to attain the therapeutic range of 30 to 100 ng/mL allowed for more effective suppression of elevated PTH in patients with SHPT, stage 3 or 4 CKD and better control of vitamin D insufficiency.

The pilot formulations and the to-be-marketed formulation (Formulation 4) are listed in the following Table 1.

Table 1. Components in development formulations and Rayaldee final formulation (Formulation 4)

		Target Percent in Fill Material (%)			
Component	Function	Formulation 1	Formulation 2	Formulation 3	Formulation 4 (Rayaldee)
Paraffin Mineral Oil Hypromellose Mono- and Di glycerides Lauroyl Polyoxylglycerides Dehydrated Alcohol Butylated hydroxytoluene					(b)(4)
Target capsule fill weight (mg) Capsule Shell					(b)(4)
Use in clinical (CL) and nonclinical studies		CTAP101-PK-0001 CTAP101-TX-0100	CTA101-CL-1005	CTAP101-CL-2004 CTAP101-PK-0006	CTAP101-PK-0012 CTAP101-TX-0102 CTAP101-PK-0014 CTAP101-CL-1011 CTAP101-CL-1016 CTAP101-CL-2008 CTAP101-CL-3001 CTAP101-CL-3002 CTAP101-CL-3003
NA, not applicable (not included in formulation)		(b)(4)			

The proposed dissolution method by the Applicant is shown in Table 2.

Table 2. Proposed dissolution method

Dissolution Procedure Apparatus: Paddle speed: Temperature: Medium:	(b)(4)
Dissolution Volume: Sample Times: Sample Pull Volume: Filter:	(b)(4)

Reviewer's Assessment:

1. Dissolution Method:

The proposed drug product is an extended release formulation. The initial dissolution method developed by the Applicant shown in Table 2 used USP II apparatus with (b)(4) (b)(4) In the current submission, the Applicant didn't include the detailed dissolution method development report to support as to how the parameters for dissolution method were derived. Furthermore, the Applicant didn't show the discriminability of the proposed dissolution method; therefore, following 74-day-letter, Biopharm comments were conveyed to the Applicant on 8/11/2015:

1. Your proposed dissolution method with USP 2 (paddle) with (b)(4) *Provide detailed dissolution method development report including the raw data in the submission to support the determination of your proposed dissolution method parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, why SDS is selected as the surfactant, and how* (b)(4) *% is determined, etc.). Also provide the complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim).*

2. Submit the data to support the discriminating ability of your proposed dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables such as the content of hypromellose). In addition, if available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent.

On Nov 30th, 2015, in response to above FDA comments, the Applicant optimized the original dissolution method, and the new dissolution method is shown in Table 3:

Table 3. New dissolution method[1]

Dissolution Parameters	Settings
Apparatus	USP 2, paddle
Dissolution Medium	0.5% SDS in 5 mM NaH2PO4 pH 6.8 (not deaerated), 500 mL
Temperature	37 °C
Stirring speed	75 rpm
Sampling time points	1, 2, 4, 6, 8, 10, 12 hours
Final spin (optional)	final spin at 250 rpm for 60 min

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(b) (4)

Finally, we recommend the Applicant to revise the dissolution acceptance criteria at 6 hr to (b)(4)%. Due to all the clinical batches are expired at the date of dissolution test with the optimized dissolution method, the Applicant needs to generate release and stability data with freshly manufactured batches, and submit these data to the Agency for review in the first Annual Report after approval. Depending on these new data, a revision to the current dissolution acceptance criteria might be necessary.

On Jan 14, an IR was conveyed to the Applicant as follows:

FDA Request:

1. Your proposed Dissolution acceptance criteria in the drug product specification "2 hours (b)(4)%" and "12 hours (b)(4)%" are acceptable based on all currently available data in the NDA. However, based on the dissolution data you provided so far, your proposed acceptance criteria "6 hours (b)(4)% and (b)(4)%" appear to be too (b)(4) for your product. We conclude that criteria "6 hours (b)(4)% and (b)(4)%" are more appropriate. Provide a revised specification to include our criteria by 18-JAN-2016 along with an agreement to update applicable sections in the NDA at the earliest opportunity to reflect the revised dissolution acceptance criteria.

2. The submitted dissolution data with optimized dissolution method were generated with expired batches on the date of dissolution test. We recommend that you obtain complete dissolution profile data (i.e., 2, 6, and 12 hrs) for all the drug product batches manufactured in the first year after approval and submit the data in the first annual report. Based on the new dissolution profile data, the dissolution acceptance criteria might be revised. Acknowledge our comment in the 18-JAN-2016 response.

In response, the Applicant provided some new release data on newly manufactured batches collected with the optimized dissolution method (shown in following tables). The Applicant committed to reviewing dissolution profile data from the first 10 commercial lots manufactured including three process validation lots together with all available stability

data up to that point in time (including 24 months on two additional lots and 18 months on a further three lots) generated using the revised dissolution method. However, the Applicant still wanted to set the dissolution acceptance criteria at 6hr to their originally proposed (b)(4)%. And they committed to revising the specification if necessary based on the new data and file a CBE30 to the Agency to communicate the proposed amended specification.

(b)(4)

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(b)(4)

[redacted]

FDA Request:

We are concerned that three of the six lots that are within their shelf life would fail the FDA recommended specification (b)(4)% at 6 hr). Furthermore, even under your proposed specification (b)(4)% at 6 h, these three lots (1422204, 1422205B, and 1498725A) (b) (4) to pass the dissolution test.

Therefore, based on the additional data submitted, we conclude that the criteria "6 hrs: (b)(4)% and (b)(4)%" appear to be more appropriate. All six lots w (b) (4) and two of these batches (1498726A and 1422205) meet the recommended criteria (b) (4). Your proposed criteria ((b)(4)% at 6 hr) are considered too (b)(4) and it will also require batches 1422204, 1422205B, and 1498725A (b) (4). Therefore, your proposed (b)(4) specification ((b)(4)%) does not offer any better solution.

Provide a revised specification to include our proposed criteria by Jan 27, 2016, along with your acknowledgement to update Module 32P51 and other related sections in the NDA to reflect the revised dissolution acceptance criteria for future implementation. Because of the high variability on release within stability batches (b) (4) ***at 6 hr during stability test, we recommend that you find out why there is*** (b) (4) ***in the dissolution. For the time being, we request you to obtain and analyze the complete dissolution profiles from the newly manufactured batches for one year upon NDA approval. Submit the new dissolution profile data to the Agency in the first annual report for review in order to finalize the dissolution acceptance criteria based on the new dissolution data generated.***

On Feb 1, 2016, the Applicant acknowledged their acceptance of the dissolution acceptance criteria of (b)(4) % at 6 hr recommended by the Agency, and updated the respective sections in the submission. Furthermore, the Applicant committed to obtaining and analyzing complete dissolution profiles from newly manufactured batches for one year upon NDA approval. These profile data and any available data will be included in the first annual report in order to finalize the dissolution acceptance criteria.

3. In vitro alcohol dose dumping study

Since the proposed drug product is a modified release formulation, an in vitro alcohol dose dumping study is recommended. The Applicant conducted the in vitro alcohol dose dumping study with calcifediol in 0.1 N HCl in the presence of up to 40% alcohol (0%, 5%, 20%, and 40%). As stated by the Applicant in the study report TTP-CZV-M0062, the Calcifediol amount released throughout the 2 hours dissolution test either not detectable (in acidic media containing 5% and 20% ethanol), or below LOQ (in acidic media containing 40% ethanol). However, there is no raw data provided with the report, and the reviewer could not evaluate the results.

Therefore, the following 74-day letter comments on in vitro alcohol dose dumping study was conveyed to the Applicant on 08/11/2015:

Submit or provide the location of the raw dissolution data in the submission for the alcohol dose dumping study. The report should include the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study.

On Sep 30, 2015, the Applicant submitted the raw data for the in vitro alcohol dose dumping study (**TTP-CZV-M0062**). Under acid condition (in 0.1N HCl medium),

calcifediol is not detectable or below the quantitation limit in the absence (baseline) and presence of up to 40% of alcohol during the 2-hr incubation study. Since most of alcohol would be consumed in the stomach, the alcohol dose dumping test conducted in acid condition is considered physiologically relevant and/or clinically meaningful.

Therefore, the above alcohol dose-dumping study in 0.1 N HCl medium is considered adequate to conclude that there is no dose-dumping for the proposed drug product. The above study results will conveyed to the OCP.

4. Extended release designation claim

Based on **21 CFR 320.25*(f)*,** the definition for extended release formulations are:

The purpose of an in vivo bioavailability study involving a drug product for which an extended release claim is made is to determine if all of the following conditions are met:

(i) The drug product meets the extended release claims made for it.

(ii) The bioavailability profile established for the drug product rules out the occurrence of any dose dumping.

(iii) The drug product's steady-state performance is equivalent to a currently marketed nonextended release or extended release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full new drug application.

(iv) The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.

The proposed drug product is designed to release calcifediol over a prolonged period to raise serum 25-hydroxyvitamin D in a gradual manner to the therapeutic range appropriate for the targeted patient population while avoiding excessive induction of CYP24A1. The immediate release oral formulation of calcifediol, which had a T_{max} of 4 to 8 hours postdose, was approved in US in 1980 as Calderol® but withdrawn from the market in 2002 for commercial reasons not associated with safety or efficacy.

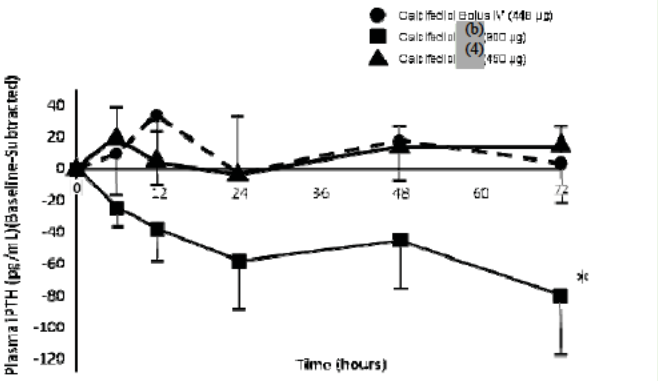
In the current submission, the Applicant conducted clinical study CTAP101-CL-1011 to compare the single dose of proposed Rayaldee (900 µg) to single dose of IV calcifediol (448 µg). Compared to the median T_{max} of 0.17 hr in calcifediol IV formulation, the proposed calcifediol product has a median T_{max} of 21 hr. AUC_{inf} of proposed drug product was approximately two-fold lower as compared with IV calcifediol, yielding a bioavailability of around 25%. Therefore, the proposed drug product met the requirement of extended release.

From the in vitro alcohol dose-dumping study conducted by the Applicant, the presence of up to 40% of alcohol after 2hr incubation at Acid Stage will not change the in vitro release

characteristic of the proposed drug product; therefore, the drug product met the requirement of no dose dumping.

As published clinical studies show, the calcifediol immediate-release formulation failed to produce clinically meaningful reductions in iPTH level (≥ 30% from pre-treatment levels) in many patients with stage 3 or 4 CKD unless a higher dose was administrated to raise serum 25-hydroxyvitamin D to supraphysiological levels (> 100 ng/ mL). As shown in Figure 7, from the comparison of one of the developed formulation 3 and calcifediol IV, the mean baseline adjusted serum iPTH reported in clinical study CTAP101-CL-2004 using 450 µg of (b)(4) formulation achieved similar effect in serum iPTH level compared to the IV calcifediol formulation, and 900 µg of (b)(4) formulation 3 achieved even greater reduction in serum iPTH from 0 to 72 hours postdose.

Figure 9 Mean Baseline-Adjusted Serum iPTH from 0 to 72 Hours(Study CTAP101-CL-2004)

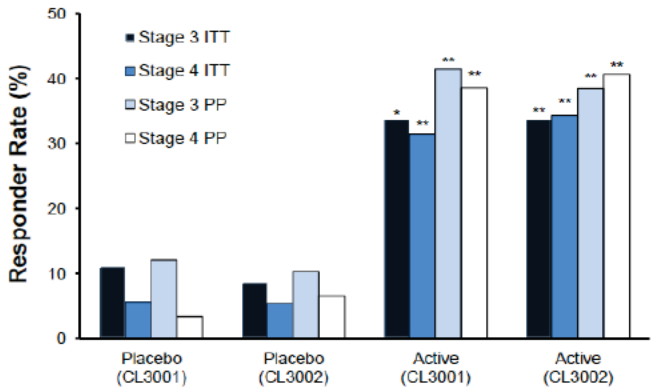


Asterisk denotes significant differences between treatment groups at $p < 0.05$ and bars indicate standard deviation.
Source: Table 10.3.1, CTAP101-CL-2004 Clinical Study Report

Both formulation 3 and formulation 4 (the proposed commercial formulation) showed lower Cmax and longer T_{max} compared to IV formulation (extended release characteristics), but the bioavailability of formulation 4 (~25%) was greater than for formulation 3 (6-11%).

Furthermore, Figure 10 below shows the response rate for plasma iPTH reduction of ≥ 30% from baseline (in which the approved oral formulation is not very efficient) after multiple dose administration of 30 µg Rayaldee daily for 12 weeks followed by 60 µg daily for 14 weeks.

Figure 10. Response Rates for Plasma iPTH Reduction of ≥30% from Baseline by Treatment Group, CKD Stage and Analysis Population in EAP (Studies CTAP101-CL-3001 and CTAP101-CL-3002)



*P<0.05 vs. placebo, **P<0.01 vs. placebo
Source: Table 14 and Table 15, CTAP101-CL-3001 Clinical Study Report and Table 14 and Table 15, CTAP101-CL-3002 Clinical Study Report.

Compared to the placebo, the current proposed drug product has a significant response rate in that plasma iPTH reduction ≥30%. Based on Figures 9 and 10, it could be seen that the proposed extended released drug product has an equivalent or even better performance compared to the approved non-extended release calcifediol drug product (IV formulation).

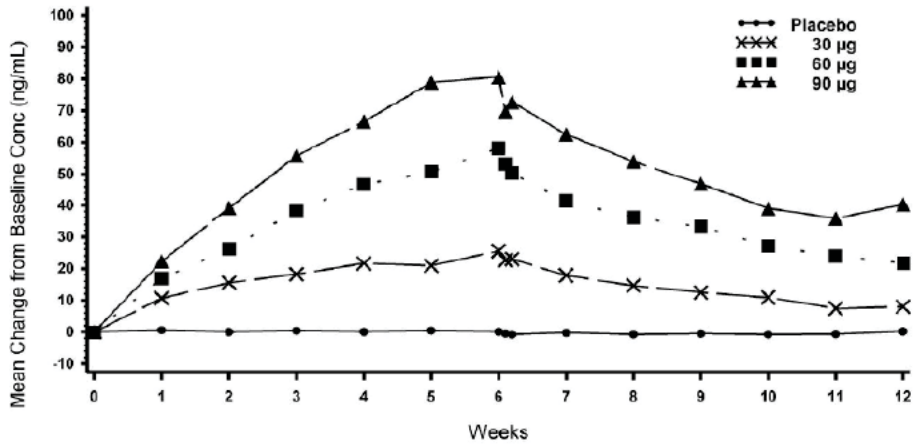
Table 11 shows the dissolution stability data for 12 units of clinical batch # 1381098. The variability in drug release from each unit tested at all-time points is small and SD is less than (b)(4)

Table 11. Dissolution Stability Data for Rayaldee Capsules, 30 µg Lot 1381098, 25°C/60% RH Storage Conditions (30 Count)

(b)(4)

Figure 11 shows the mean serum calcifediol concentration of the intended commercial formulation after multiple daily doses (30, 60, and 90 µg) for six weeks and sampled for another six weeks in clinical study CTAP101-CL-2008.

Figure 11. Mean Baseline-Adjusted Serum Calcifediol Concentrations (Study CTAP101-CL-2008)



Source: Figure 4, CTAP101-CL-2008 Clinical Study Report

Table 12 below summaries the PK parameters for serum calcifediol.

Table 12. Summary of Baseline-Adjusted Pharmacokinetic Parameters for Serum Calcifediol (Study CTAP101-CL-2008)

Parameter	Statistic	Placebo (N=29)	Rayaldee 30 µg (N=12)	Rayaldee 60 µg (N=16)	Rayaldee 90 µg (N=14)
AUC_{0-t} (ng·h/mL)	Mean	9.19	689.15	1447.80	2060.95
	(SD)	(85.66)	(238.14)	(360.22)	(586.86)
C_{max} (ng/mL)	Mean	3.58	27.75	60.33	85.69
	(SD)	(3.61)	(8.21)	(18.97)	(26.90)
t_{max} (days)	Mean	34.97	37.75	41.13	42.50
	(SD)	(30.79)	(10.41)	(5.24)	(5.06)
$t_{½}$ (days)	Mean	NA	25.32	32.67	49.62
	(SD)		(13.98)	(8.59)	(51.09)

Source: Table 18 CTAP101-CL-2008 Clinical Study Report

Serum calcifediol levels appear to show dose-proportional manner and does not reach steady level at the end of the 6-week treatment period. Linear regression analysis suggested that the proposed drug product would reach steady state after 8-9 weeks of multiple doses.

Overall, the proposed drug product shows consistent in vitro drug release between individual dosage units (Table 11), and the mean serum levels of calcifediol increases gradually in a dose-proportional manner with daily administration of Rayaldee, and then decreases thereafter (Figure 11 and Table 12), thereby providing consistent PK

performance between individual dosing.

Therefore, the extended claim for the proposed drug product is acceptable.

2. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

Applicant's Response:

Reviewer's Assessment:

As Table 1 shows, there are four pilot formulations developed by the Applicant. And the Applicant selected formulation 4 as the to-be-marketed formulation. The to-be-marketed formulation (Formulation 4) was used in the phase 1, phase 2 and phase 3 clinical studies, and the same formulation was used in the in vitro alcohol dose-dumping study as well. The clinical batches are appropriately bridged to the commercial product.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature:

1. The following optimized dissolution method is acceptable.

Dissolution Parameters	Settings
Apparatus	USP 2, paddle
Dissolution Medium	0.5% SDS in 5 mM NaH2PO4 pH 6.8 (not deaerated), 500 mL
Temperature	37 °C
Stirring speed	75 rpm
Sampling time points	1, 2, 4, 6, 8, 10, 12 hours
Final spin (optional)	Final spin at 250 rpm for 60 min

2. The Applicant acknowledged their acceptance on the Agency's recommended dissolution acceptance criteria of (b)(4)% (b)(4)% at 6hr. The final dissolution acceptance criteria proposed are therefore, acceptable:

2 hrs: (b)(4)%; 6 hrs: NLT (b)(4)% and NMT (b)(4)%; 12 hrs: NLT (b)(4)%

3. The Applicant already updated the 32P51 Drug Specification and other related sections in the submission.

4. Furthermore, the Applicant committed to obtaining and analyzing complete dissolution profiles from newly manufactured batches for one year upon NDA

approval. These profile data and any available data will be included in the first annual report in order to finalize the dissolution acceptance criteria.

5. The submitted alcohol dose dumping study is acceptable and there is no dose dumping for the proposed drug product.

6. The submitted data support the extended release claim.

Peng (Vincent) Duan, Ph.D.
Biopharmaceutics Reviewer
02/11/2016

Secondary Review Comments and Concurrence:

I concur 02/11/16

Tien-Mien Chen, Ph.D., Acting Biopharm Lead

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2.3.P.8 Stability

6. What is the proposed shelf-life for the drug product? Do the product stability studies and data support the proposed shelf life and storage conditions in the commercial container/closure system? Does the statistical evaluation of the stability data and observed trends support the proposed shelf-life?

7. Are the post-approval stability protocols and other stability commitments for the drug product adequate?

Applicant's Response:

The Applicant requested 24 months expiry period for drug product when stored in the market-representative container closure system (30 capsule and 60 capsule counts in 30 cc HDPE bottles) at the controlled room temperature.

In support, 24 months stability data for 3 registration batches were submitted in NDA amendment dated 11/30/16 (see summary in Table 7, reproduced below). Also, supportive stability data for Phase 3 and Phase 2 clinical batches were submitted in the original NDA.

Table 7 Registration Stability Batch Information

Lot	Date of Manufacture	Batch Size (Capsules)	Packaging Configuration	Storage Conditions	Available Data
1381098		(b)(4)	30-count bottles	40°C/75% RH	6 months
			30-count bottles	25°C/60% RH	24 months
1381099		(b)(4)	30-count bottles	40°C/75% RH	6 months
			30-count bottles	25°C/60% RH	24 months
			60-count bottles	40°C/75% RH	6 months
			60-count bottles	25°C/60% RH	24 months
			30-count bottles	Photostability	End of study
			Exposed capsules	Photostability	End of study
1392656		(b)(4)	30-count bottles	40°C/75% RH	6 months
			30-count bottles	25°C/60% RH	24 months
			60-count bottles	40°C/75% RH	6 months
			60-count bottles	25°C/60% RH	24 months

For the photostability study, samples were exposed to light outside of their primary package as well as within their container. Exposed capsules from four bottles were placed into a Petri dish in a single layer, and 30-count bottles (four) were stored "as is" in a light chamber. Light control samples in Petri dish and bottles (covered with foil) were also placed in the light chamber. Chamber conditions were ICH Option 2 for one cycle. The exposure entailed 1.2 million lux hours of cool white fluorescent light followed by UV light not less than 200 watt hours/m^2.

Reviewer's Assessment:

Based on the submitted stability data the requested 24 months expiry period is justified for RAYALDEE (calcifediol) extended-release capsules, 30 µg, packaged as 30 capsule and 60 capsule presentations in 30 cc HDPE bottles sealed with an (b)(4) and (b)(4) and stored at controlled room temperature, i.e., (b)(4) with excursions permitted to 15-30°C (59-86°F).

The originally submitted NDA application contained only 12 months of incomplete stability data and the following comments were forwarded to the Applicant in the IR letter dated 10/23/15:

Submit updated stability data for drug product batches representative of the commercial product, and collected with final analytical methods, to support your request for 24 months expiry period. Include results for (b)(4) ***and dissolution and indicate data points collected with the revised methods. Provide graphs with evaluation of instability trends for assay, impurities, dissolution and*** (b)(4) ***The stability data currently submitted to the NDA (12 months data for 3 registration batches and auxiliary stability data from developmental batches) do not support your request. For acceptable approaches to poolability of the data and extrapolation of the expiry period refer to the ICH Q1E Guidance on Evaluation of Stability data: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073380.pdf***

In response the Applicant submitted revised 24 month stability data and included the instability trend analyses for the assay, impurities, dissolution and (b)(4) Testing for poolability of batches was performed in accordance with Section B.2.2 of ICH Q1E, using Analysis of Covariance. Since the dissolution method was substantially revised the instability trend was discussed using data obtained with the old method, and in addition the registration lots and a number of other lots were tested close to and beyond their end of shelf life (proposed 24 months) using the optimized dissolution method and the data from these analyses were submitted – refer to the evaluation in the Biopharmaceutic section of this review.

8 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

post-approval changes are anticipated? How will the changes be reported and how will the validation studies be designed to support these changes?

Applicant's Response:

The Application does not contain a Comparability Protocol.

OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature: ADEQUATE
Overall, the submitted data are adequate to assure the quality, purity, strength and stability of the drug product and are adequate to support the request for marketing.
All initial concerns are adequately addressed by the Applicant and the request for the 24 month expiry period is adequately supported.
One outstanding Agreement pertains to controls for the mono- and di-glycerides excipient used in the extended-release formulation, with data to be submitted in the annual report – refer to list of comments below.

Eugenia Nashed, Ph.D., Chemistry Reviewer, OPPQ

Eugenia M. Nashed -S
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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300102452, cn=Eugenia M. Nashed -S
Date: 2016.02.12 12:52:13 -05'00'

Secondary Review Comments and Concurrence:
I concur with the reviewer's assessment.
Danae Christodoulou, Ph.D., Acting Branch Chief, ONDP

Danae D. Christodoulou -S
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Date: 2016.02.12 13:18:08 -05'00'

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

9. Is the applicant's claim for categorical exclusion acceptable?

10. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response:

The Applicant claims categorical exclusion for drug substance based on 21 CFR 25.31 (c) and 21 CFR 25.31 (b). The active ingredient (calcifediol) is a derivative of vitamin D3, a naturally occurring substance, and thus meets the criteria of 21 CFR 25.31 (c) such that the actions for the substance, which occurs naturally in the environment, is not expected to significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment. Additionally, the estimated concentration of the substance at the point of entry into the aquatic environmental will be significantly below 1 ppb (EIC for Rayaldee capsules is calculated as (b) (4) ppb), and thus meets the criterion for categorical exclusion under CFR 25.31 (b).

The expected introduction concentration (EIC) of the active moiety (calcifediol) into the aquatic environment is calculated as follows, using the equation provided in the Guidance for Industry (FDA, 1998):
EIC-Aquatic (ppb) = A x B x C x D
Where:
A = kg/year produced for direct use (as active moiety)
B = 1/liters per day entering POTWs*
C = year/365 days
D = 109 µg/kg (conversion factor)

* 1.214 x 1011 liters per day entering publicly owned treatment works (POTWs) (FDA, 1998)

The EIC for Rayaldee capsules is calculated as (b)(4)

Reviewer's Assessment:

The claim for the categorical exclusion is acceptable and the provided information and data are adequate for approval of the NDA application.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: ADEQUATE
Eugenia Nashed, Ph.D., Chemistry Reviewer, OPPQ

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300102452, cn=Eugenia M. Nashed -S
Date: 2016.02.12 12:52:52 -05'00'

Secondary Review Comments and Concurrence:
I concur with the reviewer's assessment.
Danae Christodoulou, Ph.D., Acting Branch Chief, ONDP

Danae D. Christodoulou -S
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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300132624, cn=Danae D. Christodoulou -S
Date: 2016.02.12 13:18:58 -05'00'

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

RAYALDEE is a vitamin D_3 analog indicated for the (b)(4) treatment of secondary hyperparathyroidism in (b)(4) with stage 3 or 4 chronic kidney disease and (b) (4) (b)(4)

The (b)(4) initial dose of RAYALDEE is 30 mcg administered once daily at bedtime. Serum calcium should be <9.8 mg/dL before initiating treatment (b)(4) (b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	RAYALDEE calcifediol extended-relase capsules	Adequate
Dosage form, route of administration	Oral Capsule	Adequate
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Extended-release formulation contained in (b) (4) capsules One strength: 30 mcg calcifediol per capsule	Adequate

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Extended-release (b)(4) capsules	Adequate
Strengths: in metric system	30 mcg calcifediol per capsule	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Blue, oval, (b)(4) capsules (b)(4) with "O" in (b)(4) (b)(4) Supplied in bottles of 30 and 60 capsules.	Adequate

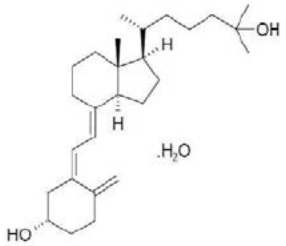
Conclusion:

The provided information is adequate from the perspective of the chemistry drug product reviewer. The Applicant was informed that originally proposed "(b)(4) (b)(4)", name should be changed to the "extended-release" designation throughout the NDA application.

#11: Description (21CFR 201.57(c)(12))

Calcifediol, USP, the active ingredient in RAYALDEE, is synthetically manufactured as calcifediol monohydrate. Calcifediol is also known as calcidiol, 25-hydroxycholecalciferol or 25-hydroxyvitamin D_3.

Calcifediol monohydrate is a white crystalline powder, has a calculated molecular weight of 418.65 and is soluble in alcohol and fatty oils but practically insoluble in water. Chemically, calcifediol monohydrate is (3β,5Z,7E)-9,10-secocholesta-5,7,10(19)-triene-3,25-diol monohydrate and its structural formula is:



RAYALDEE is formulated as (b) (4) capsules containing 30 mcg of calcifediol. Each capsule contains the following excipients: mineral oil, monoglycerides and diglycerides, paraffin, hypromellose, lauroyl polyoxylglycerides, dehydrated alcohol and butylated hydroxytoluene. The capsule shells contain modified starch, carrageenan, sodium phosphate, dibasic, sorbitol sorbitan solution, FD&C Blue #1, titanium dioxide and purified water. Medium chain triglyceride (fractionated coconut) oil is used as a lubricant during manufacture, and trace amounts may be present in the final formulation.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	RAYALDEE (calcifediol) extended-relase capsules	Adequate
Dosage form and route of administration	Oral (b) (4) capsules	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	30 mcg calcifediol per capsule	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	N/A	N/A
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	Vitamin D3 analog, prohormone	Adequate
Chemical name, structural formula, molecular weight	Calcifediol monohydrate $C_{27}H_{44}O_2$ x H_2O M.W. 418.65 g/mol	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	Adequate
Other important chemical or physical properties (such as pKa, solubility, or pH)	practically insoluble in water; freely soluble in ethanol; soluble in fatty oils.	Adequate

Conclusion:

The provided information is adequate from the perspective of the chemistry drug product reviewer.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

RAYALDEE is supplied as 30 mcg calcifediol in soft (b) (4) blue, oval capsules, imprinted (b)(4) **O** :
Bottles of 30 [*NDC 70301-1001-1*]
Bottles of 60 [*NDC 70301-1001-2*]
Store at (b)(4) C (b)(4) F); excursions permitted to 15-30°C (59-86°F) [*see USP Controlled Room Temperature*].

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	30 mcg of calcifediol per capsule	Adequate
Available units (e.g., bottles of 100 tablets)	Bottles of 30 capsules Bottles of 60 capsules	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Blue, oval, (b)(4) capsules (b)(4) with "O" in (b)(4) (b)(4) Supplied in bottles of 30 and 60 capsules.	Adequate
Special handling (e.g., protect from light, do not freeze)	N/A	N/A
Storage conditions	Store at (b)(4) C (b)(4) F); excursions permitted to 15-30°C (59-86°F)	Adequate

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	OPKO Pharmaceuticals, LLC 4400 Biscayne Blvd Miami FL 33137	Adequate

Conclusion:

The provided information is adequate from the perspective of the chemistry drug product reviewer.

2. Container and Carton Labeling

1) Immediate Container Label

(b)(4)

200 %

Reviewer's Assessment:

The revised container labels have to be submitted before approval, to change the name "(b)(4)" to "Extended-Release", as recommended to the Applicant.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The proprietary name RAYALDEE and the established name Calcifediol satisfy the font size deferential required by 21CFR 210.10(g)(2)	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength (30 mcg) is prominenty displayed on the label	Adequate
Route of administration 21.CFR 201.100(b)(3))	Oral capsules are consistent with 21.CFR 201.100(b)(3) regulations	Adequate
Net contents* (21 CFR 201.51(a))	Capsule counts (30 or 60) provided on the label	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	N/A, Solid oral dosage form	Adequate
Lot number per 21 CFR 201.18	Location for Lot # provided on the label	Adequate
Expiration date per 21 CFR 201.17	Location for Expiry provided on the label	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Rx information displayed on the label	Adequate
Storage (not required)	Starage conditions provided on the label	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	☐30 count bottles: 70301-1001-1 ☐60 count bottles: 70301-1001-2	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Provided on the label	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	OPKO Pharmaceuticals, LLC 4400 Biscayne Blvd Miami FL 33137	Adequate
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

2) Carton Labeling

The draft mock labels for the cartons have not been submitted yet. However, the Applicant provided the following NDC information:

The labeler code "70301" is assigned to OPKO Pharmaceuticals, LLC.

The following NDC numbers have been assigned by OPKO for Rayaldee:

- 30 count bottles: 70301-1001-1
- 60 count bottles: 70301-1001-2

Conclusion:

The extend of the provided information is acceptable at this point of the review, from the perspective of the chemistry drug product reviewer. However, revised container labels have to be submitted before the approval, to reflect the requested by the review team name [redacted] (b)(4) to "Extended-Release"..

Comment:

Provide revised container and carton labels with requested correction of drug product name, i.e., replace the name "[redacted] (b)(4)" with "Extended-Release".

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: ADEQUATE
Eugenia Nashed, Ph.D., Chemistry Reviewer, OPPQ

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300102452, cn=Eugenia M. Nashed -S
Date: 2016.02.12 12:53:42 -05'00'

Secondary Review Comments and Concurrence:
I concur with the reviewer's assessment.
Danae Christodoulou, Ph.D., Acting Branch Chief, ONDP

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Date: 2016.02.12 13:19:56 -05'00'

II. List of Deficiencies To Be Communicated

Drug Product

1. **We remind you of the Agreement provided in NDA amendment dated January 18, 2016, which reads as follows:**

   "The OPKO Ireland agrees to collect data, including (b)(4) values, for at least 10 distinct batches of mono- and di-glycerides ((b)(4) (b)(4)) used in the manufacturing of drug product and propose specification controls for this excipient. The first annual report (AR) will contain an interim specifications based on the analysis of available data and a justification report. Subsequent ARs will contain final specifications based on a thorough analysis of the impact of properties of the used (b)(4) excipient on the (b) (4)

2. **Provide revised container and carton labels reflecting the requested correction of drug product name, i.e., replace the name " (b)(4)," with "Extended-Release".**

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Dissolution	Impact of storage on dissolution	M	See specific discussion in the Biopharmaceutic section of this review	Acceptable	See specific discussion in the review
Controls for (b)(4) excipient	Impact of the physicochemical properties of the excipient on (b) (4)	M	Applicant agreed to perform additional studies and implement spec. controls for excipient	Acceptable	See specific discussion in the review and a comment reminding about the Agreement

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Drug content/Assay	Formulation Process Container closure	H	stability studies (b) (4)	L	none
Impurities/ degradants	Formulation Process Container closure	H	stability studies (b) (4)	L	none
Appearance	Formulation Process Container closure	H	stability studies (b) (4)	L	none
Dissolution	Formulation	H	optimize formulation release testing and stability studies	H	reference the pharmaceutical development for any change in formulation
Dissolution	Impact of storage on dissolution	M	See specific discussion in the Biopharmaceutic section of this review	Acceptable	See specific discussion in the review
Controls for (b)(4) excipient	Impact of the physicochemical properties of the excipient on (b) (4)	M	Applicant agreed to perform additional studies and implement spec. controls for excipient	Acceptable	See specific discussion in the review and a comment reminding about the Agreement
(b)(4) content	Formulation	H	optimize formulation	L	reference the formulation development for any change in formulation

The following will be conveyed to the applicant to confirm the applicant's quality proposals (in a communication separate from the Approval Letter because they do not fall in any preset category in the action letter template):

a. We acknowledge that, as proposed in the 01-FEB-2016 amendment, you will obtain and analyze complete dissolution profiles from newly manufactured product batches for one year after the NDA approval, and report the data in the first annual report in order to optimize the dissolution acceptance criteria.
b. We acknowledge that, as proposed in the 18-JAN-2016 amendment, you will collect data, including (b)(4) values, for at least ten distinct batches of mono- and di-glycerides (b)(4) used in the manufacturing of drug product and propose a specification for this excipient after the NDA approval. The first annual report will contain interim specifications based on the analysis of available data and justification. Subsequent annual reports will co inal specifications based on a thorough analysis of the impact of properties of the (b)(4) excipient (b) (4) .

Recommendation:

Approval

(This Recommendation is finalized to meet the GRMP goal and does not include the Facility Review/Manufacturing Inspection Recommendation, which is pending)

NDA 208010
Review #1
Review Date (see page 6)

Drug Name/Dosage Form	Calcifediol extended release capsule
Strength	30 mcg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Opko Holdings

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0000	5/29/2015
0002	7/8/2015
0003	7/9/2015
0008	9/30/2015
0010	11/30/2015
0013	1/19/2015
0015	1/27/2016
0016	2/1/2016

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
Application Technical Lead	Suong Tran	New Drug Products I/ONDP
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
Drug Substance	Xavier Ysern	New Drug API/ONDP
Drug Product	Eugenia Nashed	New Drug Products II/ONDP
Biopharmaceutics	Peng Duan	Biopharmaceutics/ONDP
Process	Tarun Mehta	Process Assessment II/OPF
Microbiology	Tarun Mehta	Process Assessment II/OPF
Facility	Marisa Heayn	Inspectional Assessment/OPF

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ASSESSMENT OF THE DRUG PRODUCT	
ASSESSMENT OF ENVIRONMENTAL ANALYSIS	
LABELING & PRESCRIBING INFORMATION	
ASSESSMENT OF THE PROCESS	
ASSESSMENT OF FACILITIES	
ASSESSMENT OF BIOPHARMACEUTICS	
ASSESSMENT OF MICROBIOLOGY	
LIST OF DEFICIENCIES TO BE COMMUNICATED	
ATTACHMENT	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b)(4)	II	(b)(4)	(b) (4)	Adequate	11/18/2015	by X. Ysern
	IV		(b)(4)	Adequate	12/22/2015	by T. Mehta
	III			Adequate	2/12/2016	by J. Nashed
	III					
	III					
	III					
	III					
	III					
	III					

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	18312	Authorized reference from NDA applicant (Merck)
IND	75162	

2. CONSULTS: not applicable

Executive Summary

I. Recommendation

The recommendation from the Office of Pharmaceutical Quality is for Approval (this recommendation is finalized to meet the GRMP goal and does not include the Facility Review/Manufacturing Inspection Recommendation, which is pending).

- The recommendation in this Quality Review covers all CMC information submitted in the NDA.
- The Facility/Manufacturing Inspection review will be finalized at a later date, prior to the PDUFA goal, as an addendum in Panorama.

Labeling comments will be finalized during the multi-disciplinary OND-managed labeling review.

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues: not applicable
2. Action letter language: not applicable
3. Benefit/Risk Considerations: The benefit/risk ratio is considerable because there is no calcifediol product currently marketed in the U.S. The previously approved Calderol product of NDA 018312 has been discontinued.

B. Recommendation on Post-Marketing Commitments, Agreements, and/or Risk Management Steps- not applicable

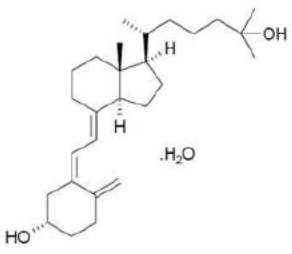
II. Summary of Quality Assessment

The applicant of NDA 208010, subject of this review, has the right of reference to NDA 018312, which results in NDA 208010 being a 505(b)(1) application but not for an NME.

A. Drug Substance

Chemical Name or IUPAC Name/Structure:

Calcifediol monohydrate is (3β,5Z,7E)-9,10-secocholesta-5,7,10(19)-triene-3,25-diol monohydrate and its structural formula is:



DMF (b)(4) is referenced for all CMC information on the drug substance. The DMF was found adequate to support this NDA on 18-NOV-2015 by ONDP/DNDAPI (X. Ysern/D. Christner).

The drug substance has the BCS designation of "insoluble" in water. It is a white (b)(4) crystal that is freely soluble in alcohol and soluble in fatty oils. (b)(4) No polymorphism has been found by IR and DSC analytical procedures.

Information on the drug substance manufacture (including starting materials, synthetis, process, container closure, and retest period of (b)(4) months at (b)(4) °C) is submitted in DMF (b)(4) (currently adequate).

The regulatory drug substance specification in the NDA is (b) (4) drug substance specification in DMF (b)(4) found adequate for this type of active ingredient based on the release and stability data.

B. Drug Product

Each extended release capsule for oral administration contains 30 mcg calcifediol: Blue oval capsule, (b) (4) with "O" in (b)(4) The fill is (b)(4) capsule shell. The fill is a (b)(4)

Excipients are mineral oil, monoglycerides and diglycerides, paraffin, hypromellose, lauroyl polyoxylglycerides, dehydrated alcohol and butylated hydroxytoluene. The capsule shell contain modified starch, carrageenan, sodium phosphate, dibasic, sorbitol sorbitan solution, FD&C Blue #1, titanium dioxide and purified water.

(b)(4)

(b)(4) was found adequate to support this NDA on 12/22/2015 by OPF/DPAII (T. Mehta/UV Venkataram).

The regulatory drug product specification is adequate based on the supporting release and stability data and ICH guidelines for this type of dosage form.

Container Closure systems: 30-count and 60-count HDPE bottles with (b)(4) closures.

Expiration Date & Storage Conditions: 24 months at room temperature, (b)(4) (b)(4)

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	[not finalized by GRMP goal; see CDTL's memo]
Non Proprietary Name of the Drug Product	Calcifediol extended release capsule
Non Proprietary Name of the Drug Substance	Calcifediol
Proposed Indication(s) including Intended Patient Population	(b)(4) treatment of secondary hyperparathyroidism in patients with stage 3 or 4 chronic kidney disease and (b) (4)
Duration of Treatment	(b)(4)
Maximum Daily Dose	60 mcg
Alternative Methods of Administration	none

D. Biopharmaceutics

The to-be-marketed drug product formulation (Formulation 4) was used in the Phases 1-3 clinical studies. The same formulation was used in the in vitro alcohol dose-dumping study, which found no dose-dumping issue. Adequate data have been provided in support of the dissolution test method and acceptance criteria for the "extended release" dosage form, including the use of 0.5% SDS (a surfactant) in the analytical procedure. Information in support of the "extended release" designation is provided in the in vivo bioavailability study report; reference is made to the Clinical Pharmacology review for details and conclusion.

E. Novel Approaches: not applicable
F. Any Special Product Quality Labeling Recommendations: not applicable
G. Life Cycle Knowledge Information (see Attachment)

OVERALL ASSESSMENT AND SIGNATURE: EXECUTIVE SUMMARY

Application Technical Lead Signature:
I concur with the reviewers' conclusions as discussed in the attached Portfolio Files. The Facility GMP review will be finalized at a later date prior to the PDUFA goal, as an addendum in Panorama.

Suong T. Tran -S

Digitally signed by Suong T. Tran -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Suong T. Tran -S, 0.9.2342.19200300.100.1.1=1300101829
Date: 2016.02.17 14:40:54 -05'00'

Suong (Su) Tran, PhD, Quality Assessment/CMC Lead, OPQ

Recommendation:
Complete Response
(including the Facility Review/Manufacturing Inspection Recommendation)

NDA 208010
Review #2
Review Date (see page 2)

Drug Name/Dosage Form	Calcifediol extended release capsule
Strength	30 mcg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Opko Holdings

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0000	5/29/2015
0002	7/8/2015
0003	7/9/2015
0008	9/30/2015
0010	11/30/2015
0013	1/19/2015
0015	1/27/2016
0016	2/1/2016

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
Application Technical Lead	Suong Tran	New Drug Products I/ONDP
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
Drug Substance	Xavier Ysern	New Drug API/ONDP
Drug Product	Eugenia Nashed	New Drug Products II/ONDP
Biopharmaceutics	Peng Duan	Biopharmaceutics/ONDP
Process	Tarun Mehta	Process Assessment II/OPF
Microbiology	Tarun Mehta	Process Assessment II/OPF
Facility	Marisa Heayn	Inspectional Assessment/OPF

Executive Summary

I. Recommendation

The recommendation from the Office of Pharmaceutical Quality (OPQ) is for Complete Response.

- This recommendation replaces the 02/17/2016 recommendation that was finalized to meet the GRMP goal with the Facility Review/Manufacturing Inspection Recommendation still pending on that date.
- The Facility Review/Manufacturing Inspection Recommendation on 03/28/2016 is for Withhold.
- There is no deficiency identified by the other review members of the OPQ team (see the 02/17/2016 review).

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues: During a recent inspection of (b)(4) (b)(4), our field investigator conveyed deficiencies to the representative of the facility.
2. Action letter language: "During a recent inspection of (b)(4) our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved."

OVERALL ASSESSMENT AND SIGNATURE: EXECUTIVE SUMMARY

Regulatory Business Process Manager Signature:

Anika A. Lalmansingh -A

Digitally signed by Anika A. Lalmansingh -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001701999, cn=Anika A. Lalmansingh -A
Date: 2016.03.28 14:13:08 -04'00'

Anika Lalmansingh, PhD, Regulatory Business Process Manager, OPQ

4 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ANIKA A LALMANSINGH
03/28/2016

Recommendation:
Approval
(including the Overall Manufacturing Inspection Recommendation)

NDA 208010
Review #3

Drug Name/Dosage Form	Calcifediol extended release capsule
Strength	30 mcg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Opko Holdings

SUBMISSION(S) REVIEWED	DOCUMENT DATE	
0000	5/29/2015	OPQ Reviews #1 and #2
0002	7/8/2015	
0003	7/9/2015	
0008	9/30/2015	
0010	11/30/2015	
0013	1/19/2015	
0015	1/27/2016	
0016	2/1/2016	
0017	2/22/2016	OPQ Review #3
0020	3/23/2016	
0021	4/22/2016	

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
Application Technical Lead	Suong Tran	New Drug Products I/ONDP
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
Drug Substance	Xavier Ysern	New Drug API/ONDP
Drug Product	Eugenia Nashed	New Drug Products II/ONDP
Biopharmaceutics	Peng Duan	Biopharmaceutics/ONDP
Process	Tarun Mehta	Process Assessment II/OPF
Microbiology	Tarun Mehta	Process Assessment II/OPF
Facility	Marisa Heayn Juandria Williams	Inspectional Assessment/OPF

Executive Summary

I. Recommendation

The recommendation from the Office of Pharmaceutical Quality (OPQ) is for Approval, including the Overall Manufacturing Inspection Recommendation dated 5/16/2016.

Review of current labeling amendments will be finalized as part of the multi-disciplinary OND-managed labeling review.

II. Summary

This current recommendation for Approval replaces the 3/28/2016 recommendation for a Complete Response which resulted from the 3/28/2016 Overall Manufacturing Inspection Recommendation for a "Withhold".

- The 3/28/2016 "Withhold" recommendation followed the FDA/ORA (b)(4) District Office's initial classification of "Offical Action Indicated" (pOAI) for the drug product manufacturing facility (b)(4). ORA placed the pOAI alert on this facility after a pre-approval and surveillance inspection of this facility (completed on (b)(4)) which found significant GMP observations.

As per the attached OPQ/OPF Facilities review, after evaluating the facility's (b)(4) response to the inspection observations and the inspection investigators' establishment inspection report (completed in early (b)(4), ORA determined that the facility's response is adequate. ORA notified OPQ/OPF on 5/11/2016 that the facility classification is now "Voluntary Action Indicated" and that the (b)(4) District Office will continue to work with the facility to resolve the inspection observations.

OVERALL ASSESSMENT AND SIGNATURE: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Suong T. Tran -S

Digitally signed by Suong T. Tran -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Suong T. Tran -S, 0.9.2342.19200300.100.1.1=1300101829
Date: 2016.05.17 09:08:24 -04'00'

Suong (Su) Tran, PhD, Quality Assessment/CMC Lead, OPQ

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: May 16, 2016

From: Juandria Williams, PhD
OPQ/OPF/DIA/Branch III

Subject:: Update on the (b)(4) Facility Status and OPF Overall Recommendation to support NDA 208010

Grace E. Mcnally -S
Digitally signed by Grace E. Mcnally -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300042045, cn=Grace E. Mcnally -S
Date: 2016.05.16 20:01:09 -04'00'

Thru: Grace McNally, Branch Chief, OPF/OPF/DIA/Branch III

To: Danae Christodolou, PhD; Branch Chief, OPQ/ONDP/Branch VI

Applicant: OPKO Ireland Global Holdings Ltd.
4400 Biscayne Blvd.
Miami, FL 33137

Establishment: (b)(4)

A pre-approval and surveillance inspection was performed at (b)(4). The (b)(4) DO initially classified the inspection OAI and determined the facility unacceptable due to significant GMP observations under the surveillance coverage. Deficiencies in the production control systems, laboratory controls, cleaning validation, standard operating procedures, deviation and OOS investigations, and employee training were observed. However no significant deficiencies specific to RAYALDEE® were observed. Due to the GMP concerns, the (b)(4) DO placed a pOAI alert on the facility in Panorama and recommended withhold; OPF further recommended a "withhold" based on the district's recommendation. A CR was submitted March 28, 2016.

The Agency received the applicant's (OPKO Ireland Global Holdings Ltd.) response to the CR on April 22, 2016, the start date of the current review cycle. The (b)(4) DO Compliance Branch proceeded to review and evaluate the inspection results, including (b)(4) response to the 483 (b)(4) and the investigator's EIR (completed (b)(4); they subsequently classified (final) the inspection as VAI. The (b)(4) DO Compliance Branch determined that the firm's response was largely adequate. The district will request additional responses from (b)(4) to address remaining concerns.

The (b)(4) DO Pre-approval Manager (PAM) notified OPF (b)(4) of the final VAI classification, removed the pOAI alert in Panorama, and recommended the facility be approved to support the NDA. Based on the district's recommendation, OPF considers the facility acceptable to support NDA 208010.

If you have any questions, please contact me at (phone number) or by email at juandria.williams@fda.hhs.gov.

Juandria Williams, PhD

Juandria Williams -S

Digitally signed by Juandria Williams -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000459158, cn=Juandria Williams -S
Date: 2016.05.16 11:46:05 -04'00'

Suong T. Tran -S
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DN: c=US o=U.S. Government ou=HHS ou=FDA ou=People cn=Suong T Tran -S 0.9.2342.19200300.100.1.1=13001001829
Date: 2015.08.05 08:25:06 -04'00'

Suong (Su) Tran, PhD
Application Team Lead

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: NDA 208010
Applicant: Opko
Chemical Type: 5

Submission Type: 505b1 (not NME, not in the Program)
Letter Date: 05/29/2015
Stamp Date: 05/29/2015

Established/Proper Name: calcifediol
Dosage Form: soft oral capsule
Strengths: 30 microgram

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			n/a
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?			• Your application referenced the Drug Master File (DMF) (b)(4) This DMF is currently deficient. Be advised that all deficiencies in the DMF must be resolved before your NDA can be approved. • (b)(4) • Provide stability data in support of the (b) (4) calcifediol (b)(4) at (b)(4)°C (you provided data at (b)(4)°C and (b)(4)°C in the NDA). • Biopharmaceutics 74-day comments can be found in the appendix at the end of this filing review.

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity[1]	☐	☒	
2.	Botanical[1]	☐	☒	
3.	Naturally-derived Product	☐	☒	
4.	Narrow Therapeutic Index Drug	☐	☒	
5.	PET Drug	☐	☒	
6.	PEPFAR Drug	☐	☒	
7.	Sterile Drug Product	☐	☒	
8.	Transdermal[1]	☐	☒	
9.	Pediatric form/dose[1]	☐	☒	
10.	Locally acting drug[1]	☐	☒	
11.	Lyophilized product[1]	☐	☒	
12.	First generic[1]	☐	☒	
13.	Solid dispersion product[1]	☐	☒	
14.	Oral disintegrating tablet[1]	☐	☒	
15.	(b)(4)	☒	☐	
16.	Liposome product	☐	☒	
17.	Biosimilar product[1]	☐	☒	
18.	Combination Product _____	☐	☒	
19.	Other _____	☐	☐	
Regulatory Considerations				
20.	USAN Assigned	☒	☐	Calcifediol
21.	End of Phase II/Pre-NDA Agreements	☒	☐	EOP2 dated 27-SEP-2013: Stability batch size, excipients and their amounts, and stability data amounts for filing. PreNDA dated 08-OCT-2014: stability data for

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

B. NOTEWORTHY ELEMENTS OF THE APPLICATION			Yes	No	Comment
					filing
22.	SPOTS		☐	☒	
23.	Citizen Petition and/or Controlled Correspondence		☐	☒	
24.	Comparability Protocol(s)[2]		☐	☒	
25.	Other		☐	☐	
Quality Considerations					
26.	Drug Substance Overage		☐	☒	
27.	Design Space	Formulation	☐	☒	
28.		Process	☐	☒	
29.		Analytical Methods	☐	☒	
30.		Other	☐	☐	
31.	Real Time Release Testing (RTRT)		☐	☒	
32.	Parametric Release in lieu of Sterility Testing		☐	☐	Not a sterile product
33.	Alternative Microbiological Test Methods		☐	☐	Not a sterile product
34.	Process Analytical Technology[1]		☐	☒	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	☒	☐	
36.		Excipients	☒	☐	
37.		Microbial	☐	☐	Not a sterile product
38.	Unique analytical methodology[1]		☐	☒	
39.	Excipients of Human or Animal Origin		☐	☒	
40.	Novel Excipients		☐	☐	Capsule shells are (b) (4) derived and previously determined by FDA to be a novel excipient. However, all ingredients of the shell are USP/NF. DMF (b)(4) is referenced for all CMC information on the capsule shell.
41.	Nanomaterials[1]		☐	☒	
42.	Hold Times Exceeding 30 Days		☐	☒	
43.	Genotoxic Impurities or Structural Alerts		☐	☒	
44.	Continuous Manufacturing		☐	☒	
45.	Other unique manufacturing process[1]		☐	☒	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	☒	[Per Biopharmaceutics reviewer's filing assessment.]
47.	New delivery system or dosage form[1]		☐	☒	
48.	Novel BE study designs		☐	☒	[Per Biopharmaceutics reviewer's filing assessment.]
49.	New product design[1]		☐	☒	
50.	Other _____		☐	☐	

[1]Contact Office of Testing and Research for review team considerations
[2]Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	Categorical exclusion request
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? For ANDAs: Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance ❑ Drug Product ❑ Appendices o Facilities and Equipment o Adventitious Agents Safety Evaluation	☒	☐	☐	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	○ Novel Excipients ❑ Regional Information ○ Executed Batch Records ○ Method Validation Package ○ Comparability Protocols				
	FACILITY INFORMATION				
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ❑ Name of facility, ❑ Full address of facility including street, city, state, country ❑ FEI number for facility (if previously registered with FDA) ❑ Full name and title, telephone, fax number and email for on-site contact person. ❑ Is the manufacturing responsibility and function identified for each facility, and ❑ DMF number (if applicable)	☒	☐	☐	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	☒	☐	☐	
	DRUG SUBSTANCE INFORMATION				
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☒	☐	☐	
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ general information ❑ manufacture ○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only ○ Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred)	☐	☐	☒	DMF (b)(4) is referenced for all CMC information on the API. The NDA includes a limited summary of information.

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials ❑ container closure system ❑ stability ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment				
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots ○ Includes complete description of product lots and their uses during development ❑ Manufacture ○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients ❑ Control of Drug Product ○ Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System ○ Include data outlined in container closure guidance document ❑ Stability ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION	☐	☐	☒	DMF (b)(4) is referenced for manufacturing information on the capsule shell preparation and encapsulation of the drug.
BIOPHARMACEUTICS [Per Biopharmaceutics reviewer's filing assessment]					

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	☒	All the BA/BE studies will be reviewed by the Office of Clinical Pharmacology (OCP).
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies*)	☒	☐	☐	The to-be-market formulation (Formulation 4) was used in the phase 1, phase 2 and phase 3 clinical studies, and the same formulation was used in the in vitro alcohol dose-dumping study as well.
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☐	☒	☐	
11.	For a (b)(4) dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☒	☐	☐	Dissolution of Rayaldee (30µg) was studied at 0, 5, 20, and 40% alcohol concentrations.
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☒	☐	☐	Clinical studies compared the Rayaldee to-be-market formulation with IV or IR formulation of calcifediol. The efficacy of multiple doses of Rayaldee is studied in the Phase 3 trial. Cmax of Rayaldee was lower which reached later than IR or IV formulation. No dose-dumping effect was reported in the alcohol dose dumping study and the results are to be discussed with OCP.
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☒	☐	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☐	☒	☐	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☒	☐	☐	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production	☐	☐	☒	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	❑ novel excipients				
17.	Are the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: ❑ Compliance to 21 CFR 601.2(a):	☐	☐	☒	

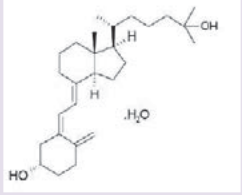
OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Kick-off meeting handout

NDA 208010
Application Type: 505(b)(1) – Not NME, not in the Program
Submission Classification: 5
PDUFA Goal Date: 3/29/2016 (Standard review)
Applicant: Opko Holdings
Trade or Proprietary Name: Pending
Established Name (USAN): Calcifediol
Dosage Form, route of administration and strength: Capsule, oral, 30 mcg
Indication: (b)(4)

Calcifediol (USP)
monohydrate of (5Z,7E)-9,10-Secocholesta-5,7,10(19)-triene-3β,25-diol



Is the Quality Section of the application fileable? Yes

This is a 505(b)(1) application but is NOT an NME, NOT in the Program. The applicant has the right of reference to the approved NDA 018312 Calderol, a discontinued product, with a letter of authorization from the applicant of NDA 18312. This is not a high-risk, orphan, or breakthrough drug.

Drug Substance: DMF (b)(4) is referenced for all CMC information on the API. The NDA includes a limited summary of information. The DMF is currently deficient and not adequate to support the pending (b)(4)). The specification is based on the USP monograph with the addition of Impurities and Residual Solvents.

Drug Product: The product is extended release for oral administration and contains 30 mcg of calcifediol in a carrageenan-derived capsule shell. There is no animal-derived excipient. The (b) (4)-derived capsule shell was previously determined by FDA to be a novel excipient because, although all the ingredients in the shell are USP/NF, their combination is novel. DMF (b)(4) is referenced for all CMC information on the capsule shell.

- (b)(4)
- Three phase 3 clinical studies were conducted in support of this NDA. The three primary stability batches were also clinical batches in these phase 3 studies. The formulation is the same for the clinical batches, stability batches, and commercial product.

Product manufacture. The product manufacturing process has (b)(4) A discussion of process changes during the IND development is included in the NDA. Any change from the phase 3/registration stability production to the proposed commercial production is deemed minor, which will be verified by the Process reviewer. The commercial

manufacturing site and scale were used to produce the phase 3 and registration stability batches. The NDA does not include the master batch records.

Drug product specification.

(b)(4)

[redacted]

74-day letter comments:

- **Your application referenced the Drug Master File (DMF) (b)(4) This DMF is currently deficient. Be advised that all deficiencies in the DMF must be resolved before your NDA can be approved.**
- (b)(4) [redacted]
- **Provide stability data in support of the (b) (4) calcifediol (b)(4) C (you provided data at (b) (4) C and (b)(4) C in the NDA).**

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

API specification:

Table 1 Specification for Calcifediol

Test	Acceptance Criteria	Analytical Procedure
Appearance	(b)(4)	
Identity		
IR spectrum	Corresponds to the spectrum of the reference standard	Ph.Eur. 1295 USP <197M>
retention time	Corresponds to the reference standard	Ph.Eur. 1295
Impurities (HPLC), in % rel		Ph.Eur. 1295
(b) (4)	(b) (4)	
Unspecified, each		
Total		
Residual Solvents (GC), in mg/kg[a]		BAI-5-2-5
(b) (4)		
Water, in % m/m		Ph.Eur. 1295 USP <921>
(b)(4)		

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Drug product composition:

Table 1 Quantitative Composition of Rayaldee Capsules, 30 µg Strength

Component	Function	Reference to Quality Standard[a]	Target Quantity (mg/capsule)	Percent of Capsule Fill (%)	Maximum Total Daily Exposure[b] (mg)	FDA Inactive Ingredients Database maximum amount listed, route of delivery, dosage form
Capsule Fill						
Calcifediol	Active Ingredient	USP	(b)(4)			NA
Paraffin	(b) (4)	NF				(b) (4)
Mineral Oil		USP				
Hypromellose		USP				
Mono- and Di-glycerides		NF				
Lauroyl Polyoxylglycerides		NF				
Dehydrated Alcohol		USP				
Butylated Hydroxytoluene		NF				
Core capsule weight	NA	NA				NA

Component	Function	Reference to Quality Standard[a]	Target Quantity (mg/capsule)	Percent of Capsule Fill (%)	Maximum Total Daily Exposure[b] (mg)	FDA Inactive Ingredients Database maximum amount listed, route of delivery, dosage form
Capsule Shell						
Medium-Chain Triglycerides[c]	(b)(4) lubricant	NF	NA	NA	NA	NA
(b)(4) Soft Capsule Shell[d]	Capsule	See DMF[d]	(b)(4)	NA	(b)(4)	NA
(b)(4)				NA	NA	NA
			NA	NA	NA	NA
Total capsule weight	NA	NA	(b)(4)	NA	NA	NA

NA not applicable

[a] USP/NF: United States Pharmacopeia/National Formulary, current edition

[b] Based on a maximum total daily dose of 2 capsules, (60 µg total)

[c] Also known as fractionated coconut oil; is used as an (b)(4) lubricant during the (b)(4) process

[d] The soft capsule shell contains modified starch, carrageenan, dibasic sodium phosphate, sorbitol sorbitan solution, FD&C Blue #1, titanium dioxide and purified water. Details regarding the colorant and other excipients utilized in the manufacture of the capsule shell may be found in (b)(4) DMF (b)(4)

(b)(4)

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Drug product specification:

Table 1 Release and Shelf Life Specification for Rayaldee Capsules 30 µg Strength

Attribute	Analytical Method[a]	Analytical Method Type	Acceptance Criteria
Capsule Appearance	PDR-ATM-CZV-0007/687	Visual	Uniform blue oval capsules, (b) (4) in white with "O", filled with (b) (4), (b) (4) material
Identification			
HPLC retention time	PDR-ATM-CZV-0009/1413	HPLC	Consistent with retention time of reference standard
UV absorbance spectrum	PDR-ATM-CZV-0009/1413	HPLC	Consistent with absorbance spectrum of reference standard
Assay			
(b)(4)	(b)(4)	HPLC HPLC	(b)(4)
Uniformity of Dosage Unit	PDR-ATM-CZV-0009/1413	HPLC	As per USP <905>
Impurities			
Single specified, each	PDR-ATM-CZV-0011/1412	HPLC	(b)(4)
Single unspecified, each	PDR-ATM-CZV-0011/1412	HPLC	

			(b)(4)
Total	PDR-ATM-CZV-0011/1412	HPLC	
Dissolution	PDR-ATM-CZV-0012/1410	USP Apparatus 2/UPLC	
			(b)(4)
			(b)(4)
Microbial Limits Testing			
Total aerobic microbial	279/USP <61>, <62>	Microbial enumeration test	≤1000 cfu/g
Total yeast and mold	285/USP <61>, <62>		≤100 cfu/g
E. coli	287/USP <61>, <62>	Test for specified microorganism	Absent in 1g
Salmonella sp.	286/USP <61>, <62>		Absent in 10 g
S. aureus	288/USP <61>, <62>		Absent in 1 g
P. aeruginosa	289/USP <61>, <62>		Absent in 1 g

[a] Where two method numbers are indicated (method 1/method 2), both methods are equivalent however a different method identification is used at different testing locations.

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Appendix:

Biopharmaceutics Summary [by Peng Duan/Tien Mien Chen]

The pilot formulations and the to-be-market formulation (Formulation 4) are listed in the following table:

Table 3 Components in Development Formulations and Rayaldee Capsules

		Target Percent in Fill Material (%)			
Component	Function	Formulation 1	Formulation 2	Formulation 3	Formulation 4 (Rayaldee)
Paraffin	(b)(4)	(b)(4)			(b)(4)
Mineral Oil					
Hypromellose					
Mono- and Di glycerides					
Lauroyl Polyoxylglycerides					
Dehydrated Alcohol					
Butylated hydroxytoluene					
Target capsule fill weight (mg)					
Capsule Shell		Hard gelatin	Hard gelatin	(b)(4) Soft Capsule	(b)(4) Soft Capsule
Use in clinical (CL) and nonclinical studies		CTAP101-PK-0001 CTAP101-TX-0100	CTA101-CL-1005	CTAP101-CL-2004 CTAP101-PK-0006	CTAP101-PK-0012 CTAP101-TX-0102 CTAP101-PK-0014 CTAP101-CL-1011 CTAP101-CL-1016 CTAP101-CL-2008 CTAP101-CL-3001 CTAP101-CL-3002 CTAP101-CL-3003
NA, not applicable (not included in formulation)					

(b)(4)

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The proposed dissolution method is as follows:

Dissolution Procedure	(b)(4)
Apparatus:	
Paddle speed:	
Temperature:	
Medium:	
Dissolution Volume:	
Sample Times:	
Sample Pull Volume:	
Filter:	

The Applicant provided the dissolution method analytical (PDR-ATM-CZV-0012) and validation method (TTP-CZV-M0050). The Applicant also conducted the alcohol dose dumping study (TTP-CZV-M0062).

Biopharm recommendations and 74-day letter comments

It is fileable from the perspective of Biopharmaceutics.

74-day letter comments to be conveyed to the Applicant:

1. Submit or provide the location of the raw dissolution data in the submission for the alcohol dose dumping study. The report should include the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study.

2. Your proposed dissolution method with USP 2 (paddle) with (b)(4) Provide detailed dissolution method development report including the raw data in the submission to support the determination of your proposed dissolution method parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, why SDS is selected as the surfactant, and how (b)(4) is determined, etc.). Also provide the complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim).

3. Submit the data to support the discriminating ability of your proposed dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables such as the content of hypromellose). In addition, if available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent.

4. Your proposed dissolution acceptance criteria are:

(b)(4)

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The current proposed specification at 6 hr (b)(4)%) is (b)(4) than the regular range (mean (b)(4)% allowed for the 6 hr time point, therefore, it is not acceptable. For (b)(4) drug products, without an established successful IVIVC study to support a (b)(4) we recommend a mean (b)(4)% boundary of dissolution acceptance criterion at 6 hr time point. If there is any revision on the current proposed dissolution method, the dissolution acceptance criteria will need to be reassessed and submitted for review with the supporting dissolution profile data.

Furthermore, while setting the specification, time points should cover the early, middle, and the late stages of the dissolution profile. The last time point should be the time point where at least (b)(4)% of drug has dissolved. If the maximum amount dissolved at late stages is less than (b)(4)%, the last time point should be the time when the plateau of the dissolution profile has been reached. The current proposed acceptance criterion at 12 hr is NLT (b)(4)%, but the maximum amount dissolved at this time point is (b)(4) than (b)(4)%. Therefore, it is recommended that the specification at 12 hr be set NLT (b)(4)%.

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