CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212306Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 212306
Review #1

Drug Name/Dosage Form	XPOVIO™ (Selinexor) Tablets
Strength	20 mg
Route of Administration	Oral
Rx/OTC Dispensed	R_x
Applicant	Karyopharm Therapeutics Inc.
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	05-Aug-18	All
Amendment	24-Oct-18	DS, Process
Amendment	08-Nov-18	DS, Process
Amendment	14-Dec-18	Process
Amendment	03-Dec-18	DP
Amendment	10-Dec-18	DP

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Sharron Kelly	Suong Tran
Drug Product	Rajiv Agarwal	Anamitro Banerjee
Process	Yifan Wang	David Anderson
Microbiology	n/a	n/a
Facility	Yifan Wang	David Anderson
Biopharmaceutics	Akm Khairuzzaman	Banu Zolnik
Regulatory Business Process Manager	Rabiya Hadier	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	Rajiv Agarwal	Anamitro Banerjee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type IV			n/a	8/24/18	Adequate information provided in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	114042	Investigational Studies

2. CONSULTS

N/A

Executive Summary

1. Recommendations and Conclusion on Approvability

OPQ recommends APPROVAL of NDA 212306 for Selinexor Tablets 20 mg. As part of this action, OPQ grants a (b) (4) re-test period for the drug substance when stored at (b) (4) and a 36-month expiration period for the drug product when stored at "20°C to 25°C (68°F to 77°F) excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]". There are no outstanding issues and no post-approval quality agreements to be conveyed to the applicant.

2. Summary of Quality Assessments

1. Product Overview

NDA 212306 was submitted for Selinexor Tablets 20 mg in accordance with section 505(b)(1) of the Food, Drug and Cosmetic Act. Selinexor is an orally bioavailable, potent, selective, first-in-class, small molecule XPO1 inhibitor. The drug product, Selinexor Tablets 20 mg is designed to be used with dexamethasone for the treatment of patients with relapsed/refractory multiple myeloma (RRMM) who have received at least 3 prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor (PI), at least one immunomodulatory agent (IMiD), an anti-CD38 monoclonal antibody (mAb), and to their most recent treatment regimen. Selinexor is an NME that was originally investigated under IND 114042 and was granted orphan (January 2015) and fast-track designation (April 2018) for the treatment of multiple myeloma. The applicant requested and was been granted a priority review of this application.

Selinexor is a small achiral BCS class 2 molecule that is manufactured by (b) (4) The drug product, Selinexor tablets, 20 mg is an immediate release oral dosage. The drug product is presented as blue, bi-convex, round, film-coated tablet with "K20" debossed on one side and nothing on the other side. Each tablet contains 20 mg of the active, microcrystalline cellulose (b) (4) croscarmellose sodium, colloidal silicon dioxide, povidone K30, sodium lauryl sulfate, microrystalline cellulose (b) (4) and magnesium stearate.

The recommended dosing regimen for Selinexor is 80 mg twice weekly until disease progression or unacceptable toxicity. The dose may be reduced based upon tolerability to 60 (b) (4) mg.

Based on the information provided in this application (original submission and in responses to information requests), OPQ considers all review issues adequately addressed and potential risks to patient safety, product efficacy, and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 212306 and grants a (b) (4) re-test period for the drug substance and a **36**-month expiration period for the

drug product (b) (4)

Proposed Indication(s) including Intended Patient Population	Indicated in combination with dexamethasone for the treatment of patients with relapsed refractory multiple myeloma who have received at least three prior therapies and whose disease is refractory to at least one proteasome inhibitor, at least one immunomodulatory agent, and an anti-CD38 monoclonal antibody.
Duration of Treatment	until disease progression or unacceptable toxicity
Maximum Daily Dose	100 mg/day
Alternative Methods of Administration	None

2. Quality Assessment Overview

Drug Substance

Selinexor is a small, achiral, molecule that has low solubility and high permeability drug (BCS class 2). Selinexor is manufactured by (b) (4) It is a white to off-white non-hygroscopic solid that is very soluble in DMSO, freely soluble in methyl-tetrahydrofuran, soluble in ethanol, sparingly soluble in acetonitrile and isopropyl alcohol and practically insoluble in water.

(b) (4)

Polymorph screenings of the drug substance were performed (b) (4) A summary of the results of the polymorphic studies is included in the drug substance review.

The drug substance is stored (b) (4)

The drug substance specification include tests and acceptance criteria for description, identification (IR and UV), assay, related substances, residual solvents, water content, residue on ignition, elemental impurities, microbial limits and particle size distribution.

Specifications and acceptance criteria for the drug substance are consistent with ICH Q6A and are adequate to ensure the quality of the drug substance as it relates to the safety and efficacy of the drug product. All analytical methods are described in adequate detail and are appropriate for their intended use. All validation parameters - system suitability and system precision, specificity, linearity, range, precision, accuracy, ruggedness, robustness, and stability of solutions are provided in the NDA.

Batch analyses data are included for seventeen batches of the drug substance. The batches range in size from (b) (4) and were manufactured at (b) (4) All results were well within the release specifications with a consistently high purity. No trends are apparent in the release data during the development of this product.

Primary stability studies were conducted on for three primary registration batches (27001369, 27001370, and 27001373) and one clinical batch (27001383) of the drug substance. (b) (4) . The primary stability batches were manufactured at the proposed commercial site via the proposed commercial route and packaged in (b) (4) The batches ranged from pilot scale (registration and clinical batches) to commercial scale (validation batches). In addition to long-term and accelerated stability data, the applicant also included forced degradation and photostability results.

The available stability data for the registration batches demonstrated no notable changes (b) (4) The applicant requested (b) (4) retest for drug substance. The long term and accelerated stability data, forced degradation studies and stress testing support the proposed retest of (b) (4) for the drug substance when stored at (b) (4) and packaged (b) (4) The appropriateness of the container closure system for ensuring the stability of the drug substance was demonstrated through stability studies.

The application is recommended for approval from a drug substance perspective.

Drug Product and Drug Process

The drug product, Selinexor tablets, 20 mg is an immediate release oral dosage. The drug product is presented as blue, bi-convex, round, film coated tablets with "K20" debossed on one side and nothing on the other side Each tablet contains 20 mg of the active ingredient Microcrystalline Cellulose (b) (4), Croscarmellose Sodium, Colloidal Silicon Dioxide, Povidone K30, Sodium Lauryl Sulfate, Microrystalline Cellulose (b) (4) and Magnesium Stearate.

The drug product has a recommended dose of 80 mg on days 1 and 3 of each week with a MDD of 100 mg.

Selinexor tablets, 20 mg are manufactured by Catalent CTS, LLC. at a commercial batch size of (b) (4) Clinical batches sizes ranged from *ca.* (b) (4) tablets. Registration batch sizes ranged from of (b) (4) tablets. The proposed commercial batch size of (b) (4) tablets represents a (b) (4) from the registration batch size.

The drug product was manufactured at (b) (4) The manufacturing process included well defined in-process controls, process parameters and critical process parameters and is summarized in the process IQA. The proposed process parameters and in-process controls were appropriate, justified and described in sufficient detail. The applicant demonstrated the suitability of the manufacturing process for the drug product at commercial scale.

The drug product will be packaged in 4, (b) (4) or 8 count individually seal blister sleeves. (b) (4) The lidding material is comprised of 20µm aluminum foil with a heat-seal coating on one side and a print primer on the other side. The product contact surface is (b) (4) and the heat seal coating of the lidding.

The drug product specifications included appearance, identification, assay, content uniformity, related substances, dissolution, (b) (4) and microbial limits. The applicant conducted a risk assessment for the potential sources and levels of elemental impurities as per (b) (4) The results of the risk assessment were acceptable and therefore the test for elemental impurities in the drug product release specifications was omitted and is not required (See drug product review for details). The drug product specifications are consistent with ICH Q6A and are based on batch analyses and stability data. The drug product specifications provide adequate controls to ensure the quality of the drug product throughout the product expiry. The proposed specification and acceptance criteria for the drug product, together with controls for impurities in the drug substance are adequate to ensure that the critical quality attributes of this product are well controlled.

Stability studies were executed in accordance with the ICH 1A and Q1B. In support of the proposed 36 month expiry, the applicant provided 24 months of primary stability data for three registration batches of the drug product (L0502484, L0502485 and L0503266), 36 months of data for clinical batch L0409913 and 44 months for clinical batch L0408660. All batches were manufactured at the commercial manufacturing site, using a manufacturing process that is representative of the commercial process and

packaged blisters ((b) (4) and 8 count). The samples were stored under the long-term (25°C/60% RH), accelerated (40°C/75% RH), at 5°C/60% RH and 30°C/65% RH. The results from primary stability studies demonstrated no substantial changes in the appearance, assay, dissolution, hardness, polymorphic form, related substances or (b) (4) Moreover, in addition to the primary stability studies, bulk, photostability and forced degradation studies were also completed in support of the proposed expiry (see drug product review for details).

The available stability data shows consistency over time and support the proposed expiry. Based on the 24 months of stability data included in this application for Selinexor Tablets 20 mg, Karyopharm Therapeutics, Inc. proposed and the FDA accepts the expiration dating period of **36 months** for the drug product when stored at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

NDA 212306 is recommended for approval from a drug product and drug process perspective with an assigned drug product expiry of 36-months.

Biopharmaceutics

There were 3 formulations (one capsule and two tablet formulations) used throughout development. The tablet formulations were referred to as TF1 and TF2. Tablet Formulation 1 (TF1) was manufactured by (b) (4) Tablet Formulation 2 (TF2) was manufactured by (b) (4) . The Applicant stated that the three formulations are functionally bioequivalent. The TF2 formulation used in the pivotal Phase II/III clinical study and the commercial drug product formulation are slightly different. The formulation used in the pivotal Phase II/III clinical study (TF2.2) and the proposed commercial formulation (TF2.3) are identical with respect to (b) (4) however, they differ with respect to (b) (4) The TF2.2 formulation utilized (b) (4) and the TF2.3 formulation utilized (b) (4)

The biopharm review of this application focused on:

1. the acceptability of the proposed dissolution method and acceptance criterion for the routine QC testing of the proposed drug product at batch release and on stability
2. bridging of clinical product to the to the to-be-marketed product.

Dissolution Specification and Method: The dissolution method includes a USP Apparatus II (Paddle) at 75 rpm in 900 mL of 10 mM Citric Acid Buffer at pH 4.5 with (b) (4)% SDS at 37ºC. The originally proposed dissolution acceptance criterion was Q= (b) (4)% in (b) (4) minutes; however, during the review cycle the acceptance criterion was revised (per biopharm request) to Q= (b) (4)% in 30 minutes. The Applicant investigated the discriminating capability of the dissolution method with respect to particle size and without disintegrant. It was concluded that the method has limited discriminating capability with respect to API PSD variation but still it can show some difference in dissolution rate with respect to significant PSD variation.

Bridging: With the exception of (b) (4) the Phase III tablets are identical to the proposed commercial product. The applicant provided dissolution profile comparison data (*f2*) (b) (4) The data fully supports the bridging between the Phase III and proposed commercial product.

Based on the information provided (i.e. dissolution profile data for pivotal clinical batches and stability data), the proposed dissolution method and revised dissolution acceptance criterion were considered acceptable for batch release and stability testing for the drug products. Based on the dissolution profile comparison, it was concluded that bridging between of the Phase III product to the proposed commercial product is established. Accordingly, this application is recommended for approval from a biopharmaceutics perspective.

Facilities

NDA 212306 included 11 sites and all sites were listed as ready for inspection:

- (b) (4)
- **Integrated Commercialization Solutions, LLC**- (b) (4) (b) (4), re-label, (b) (4)
- **Catalent CTS, LLC.** - drug product manufacture, (b) (4)
- **Carton Service Incorporated** (b) (4) - drug product labeling and packaging

All facilities listed in NDA 212306 were deemed acceptable for the responsibilities listed in the application. Accordingly, NDA 212306 is recommended for approval from a compliance perspective.

Environmental Assessment

The applicant provided a claim for categorical exclusion and a statement of no extraordinary circumstances under 21 Code of Federal Regulations (CFR) Sections 25.31(b). The categorical exclusion cited is appropriate based on the estimated amount of drug to be produced for direct use. The claim of categorical exclusion is therefore acceptable and granted.

3. **Special Product Quality Labeling Recommendations (NDA only)**

n/a

4. **Final Risk Assessment (see Attachment)**

Attached.

86 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

LABELING (NDA 212306)

R Regional Information

1.14 Labeling

Labeling & Package Insert

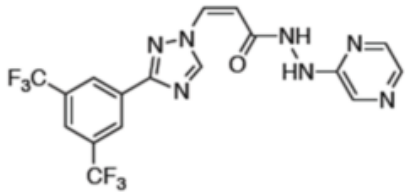
DESCRIPTION section:

11 DESCRIPTION

XPOVIO (selinexor) is an orally available [(b) (4)]

[(b) (4)] Selinexor is (2*Z*)-3-{3-[3,5-bis(trifluoromethyl)phenyl]-1*H*-1,2,4-triazol-1-yl}-*N*'-(pyrazin-2-yl)prop-2-enehydrazide. It is a white to off-white powder [(b) (4)] has the molecular formula $C_{17}H_{11}F_6N_7O$ and a [(b) (4)] molecular mass of 443.31 g/mol.

The molecular structure is shown below:



Each XPOVIO (selinexor) tablet contains 20 mg of selinexor as the active ingredient.

XPOVIO tablets are blue, bi-convex, round, film coated tablets with "K20" debossed on one side and nothing on the other side. The inactive ingredients are microcrystalline cellulose, croscarmellose sodium, povidone K30, sodium lauryl sulfate, colloidal silicon dioxide, magnesium stearate, Opadry 200 clear and Opadry II blue.

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section:

16 HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

i) Is the information accurate? ☐ Yes ☒ No

If "No," explain.

ii) Are the storage conditions acceptable? ☐ Yes ☒ No

If "No," explain.

Refer to reviwer's assessment

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended starting dose of XPOVIO is 80 mg (b) (4)
[see Clinical Studies (14.1)].

The recommended starting (b) (4) of (b) (4) dexamethasone is 20 mg taken orally (b) (4)
(b) (4)

Each XPOVIO dose (b) (4)
(b) (4)

If a XPOVIO dose is missed or delayed, instruct patients to take their next dose at the regularly scheduled time. If a patient vomits a dose of XPOVIO, the patient should not repeat the dose, patients should take the next dose on the next regularly scheduled day.

(b) (4)

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)?
☐ Yes ☐ No ☒ N/A

If "No," explain.

Refer to reviwer's assessment

R Regional Information

1.14 Labeling

Commercial packagings:

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Secondary Container Label: (Carton)

(b) (4)

Reviewer's Assessment:

1. The labeling of container labels is per labelling tool, guidances and CFR to have the most current information of the labels.

2. Child resistant closure statement per following guidance has been included in the physician's labeling (PI).

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM569607.pdf

3. Per 21 CFR 201.56 all relevant information pertaining to the each section of the labeling have been provided on the labels. However, the information is revised/rearranged in labeling for clarity.

4. 100 mg dose presentation is not yet finalized by the clinical. If this happens, labeling will be reviewed by the ATL and included in their memo.

5. The PI labeling, once the CMC recommendations are implements, will be adequate.

6. A final version of the agreed upon PI (with DMEPA's editorial chages) labeling will be reviewed by the ATL and included in their memo.

7. Storege temperature, per oncology CMC team SOPs, will be revised as follows:

Revise the storage temp from (b) (4) (b) (4) *in all labels and provide the colored mock ups.*

Conclusions:
The container/carton lables, once the storage temperature is implements, will be adequate.
The PI labeling, once the CMC recommendations are implements, will be adequate.

Primary Labeling Reviewer Name and Date:

Rajiv Agarwal, Ph.D, 10-DEC-2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Anamitro Banerjee, PhD, December 10, 2018

Rajiv Agarwal

Digitally signed by Rajiv Agarwal
Date: 12/13/2018 11:34:42AM
GUID: 504fa29c0000100b83d3aaa4905783c1

Anamitro Banerjee

Digitally signed by Anamitro Banerjee
Date: 12/13/2018 12:51:47PM
GUID: 5075764700003844b7bc89632228509f

BIOPHARMACEUTICS

Application No: NDA 212306 - Original submission dated 06/29/2018, fast track designated
Drug Product Name/Strength: XPOVIO™ (Selinexor) Tablets, 20 mg
Route of Administration: Oral
Applicant Name: Karyopharm Therapeutics Inc.

Submission: Karyopharm Therapeutics, Inc. is seeking approval for XPOVIO™ (Selinexor) Tablets, 20 mg, under the 505 (b)(1) path through granted fast track designation. The drug is a first in class oral XPO1 inhibitor, in combination with low-dose dexamethasone. The proposed drug product is a film coated immediate release tablet for the treatment of relapsed refractory multiple myeloma (RRMM).

This 505(b)(1) NDA relies in part on findings of safety, efficacy and pharmacokinetics from 8 clinical trials, out of which 7 clinical trials were conducted with patients with solid tumors[1]. Pharmacokinetic studies were conducted during Phase I studies (food effect, PK characterization) only in patients with advanced metastatic solid tumor.

REVIEW SUMMARY

The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting; **1)** the proposed dissolution method and acceptance criterion, **2)** biowaiver request, and **3)** bridging of Phase III to Commercial product, and bridging of current to new manufacturing site.

1) DISSOLUTION TEST:

Dissolution Method and Acceptance Criterion: The Applicant's proposed dissolution method [*USP apparatus II (Paddle) at 75 rpm; 900 mL of 10 mM Citric Acid Buffer, pH 4.5 with 0.5% SDS at 37°C*] and revised acceptance criterion of Q= (b) (4)% at 30 are **acceptable** for release and on stability.

2) BIOWAIVER REQUEST:

There is no biowaiver request and nor needed in the application since there is only one strength (20 mg) for this drug product.

***3)* BRIDGING**

Bridging of Clinical to to-be-marketed Drug Product: The formulation of the Phase III-film coated tablets is the same as the to-be-marketed tablets, except for the coating color (b) (4)

[1] \\cdsesub1\evsprod\NDA212306\0001\m1\us\12-cover-letters

will be used in commercial product). The provided dissolution profile comparison data (f_2) (b) (4) fully support the bridging between Phase III and to-be-marketed drug products. Additionally, the post change products are currently dosed in the ongoing study (KCP-330-009). The bridging is ***Acceptable.***

Bridging of Manufacturing Sites for Clinical Supplies and Commercial Drug Product: The manufacturing site is the same for the commercial product and there no further bridging is required.

RECOMMENDATION:

Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 212306 for Selinexor Tablets, 20 mg, is recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

➢ DRUG PRODUCT:

The proposed drug product is a film coated immediate release tablet. The formulations contain the active ingredient, Selinexor. Inactive ingredients are microcrystalline cellulose, croscarmellose sodium, povidone, colloidal silicon dioxide, magnesium stearate and film coating color components. The manufacturing process utilizes (b) (4)

➢ *BCS DESIGNATION*

The drug, is a poorly soluble drug as demonstrated in the following table for solubility.

Medium	1 hour		24 hours	
	Solubility (mg/mL)	Solubility (mg/vessel)	Solubility (mg/mL)	Solubility (mg/vessel)
0.1N HCl	0.03	27.44	0.029	25.39
0.1N HCl with 0.1% SDS	0.743	668.7	0.726	653.76
0.1N HCl with 0.25% SDS	0.759	682.81	0.717	645.4
10 mM Citric Acid pH 4.5 with 0.25% SDS	0.149	133.92	0.15	134.65
10 mM Citric Acid pH 4.5 with 0.5% SDS	0.33	296.7	0.334	300.32
10 mM Citric Acid pH 4.5 with 1.0% SDS	0.661	594.56	0.665	598.08

In vitro Caco-2 and MDCKII permeability assays demonstrated that selinexor is highly permeable, therefore, the disintegration and dissolution rate of the tablet may impact the rate the absorption and bioavailability. The absolute bioavailability has not been determined. PK parameters are as follows: t_{max}: earliest is 1 hr., 95% protein bound, parent selinexor is the main moiety in plasma, no significant food effect.

➢ *DISSOLUTION INFORMATION:*

Proposed Dissolution Method and Acceptance Criterion: The dissolution method and dissolution acceptance criterion proposed by the Applicant for the proposed drug product are presented below.

USP Apparatus	Speed (RPMs)	Medium	Volume/Temp (mL/°C)	Analytical Method	Proposed Revised Acceptance Criteria
II (Paddle)	75	10 mM Citric Acid Buffer, pH 4.5 with 0.5% SDS	900/37	HPLC	Q= (b) (4)% at 30 min

- ***DISSOLUTION METHOD DEVELOPMENT***

(b) (4)

2 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

➢ ***EFFECT OF API PSD ON BIOAVAILABILITY***

Applicant has investigated the impact of API PSD variation on dissolution and bioavailability. The bioavailability was done in single dose non-GLP animal (dog) PK study utilized here in this review as a supporting data. The following table summarizes the PSD data used in such study:

Selinexor Drug Substance Lot Number	**Manufacturer, Use**	**d10 (µm)**	**d50 (µm)**	**d90 (µm)**
27001369 (L0502332)	(b) (4), Clinical			(b) (4)
1405463 (L0408106)	Clinical			
1371-BS-099-1	R&D			
Selinexor Fraction #1,	(b) (4)			
Selinexor Fraction #2,				
Selinexor Fraction #3,				

Figures 3 & 4 show dissolution data profile as a function of API PSD variation and animal PK profile.

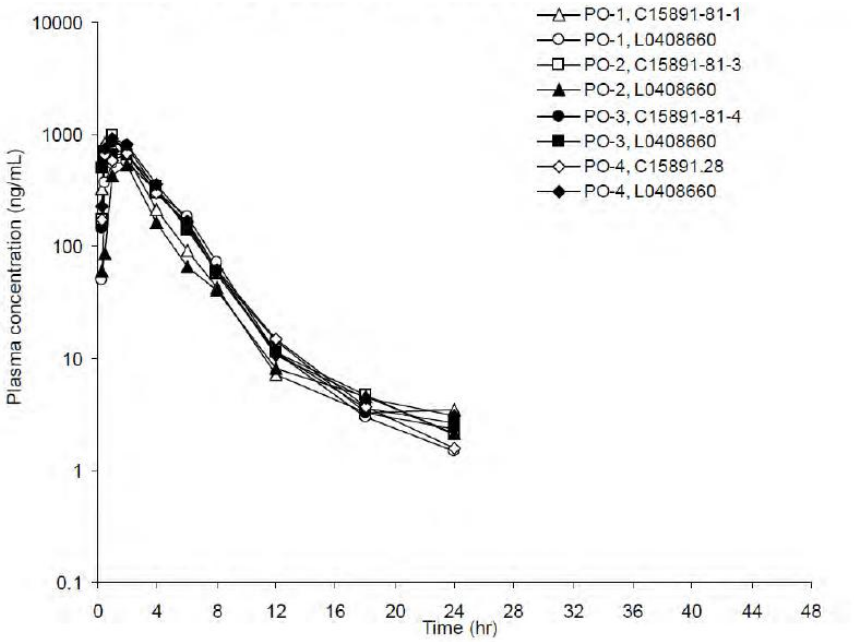


Fig. 4. Effect of API PSD variation on PK in dog model (Official method)

Reviewer's Assessment: **ADEQUATE**

The drug is poorly soluble and highly absorbable. PSD variation can directly impact total surface area and thus can impact dissolution rate as demonstrated in the above figure. The dissolution method has limited discriminating capability with respect to API PSD variation (since the method has certain amount of surfactant in its medium), but still it can show some difference in dissolution rate with respect to significant PSD variation. Initial information revealed that all clinical and registration batches used API PSD ranging D90 of (b) (4) µm and showed drug release of at least (b) (4)% in 30 minutes. Therefore, although the animal model (dog) showed no differences in bioavailability with respect to PSD variation, its bioavailability risk in human is unknown in absence of human data. Applicant (b) (4) the PSD limit based on the API PSD data from the lots used in the clinical and registration batch manufacture. The following IR question were sent out:

IR # 1: The FDA acknowledges the dissolution data and animal PK study to show the impact of API PSD variation on bioavailability. Since selinexor is a poorly soluble drug, and all clinical/registration batches used API lots that had PSD data ranging D90: (b) (4) µm, animal PK data is not conclusive to support (b) (4) API PSD acceptance criteria, D90: (b) (4) µm. Therefore, based on the clinical batch API lots, establish a three tier particle size distribution limit.

Applicant's Response: The applicant has responded on 10/24/2018. Applicant has now proposed the following PSD limit based on the data provided below.
PSD limit: D90-NMT (b) (4) µm, D50-NMT (b) (4) µm, and D10-NMT (b) (4) µm.
PSD data for selinexor lots # 1405463, 1405531, 27001369, and 27001370.

	1405463	1405531	27001369	27001370	AVE (µ)	SD (σ)	µ + σ[a]	µ + 2σ[a]	µ + 3σ[a]
d(10) µm	(b) (4)								
d(50) µm									
d(90) µm									

[a] Ave (µ) + 1, 2, and 3 standard deviations (σ)

Reviewer's Evaluation: Unacceptable.
While the proposed limit (based on 3 sigma values) is numerically right, but it is not clear whether the lot # 1405463 and 1405531 (b) (4) were used in the clinical and registration batches. According to Applicant's justification provided under the module 3.2.S.4.5.2.10, "*Particle size distributions during the clinical development using registration batches of selinexor API in the tablet core formulation (TF2), which was being scaled for commercial use, have d(10) ranging from* (b) (4) *µm and d(90) ranging from* (b) (4) *µm using the validated particle size method".* Therefore, if drug product is manufactured with such a (b) (4) PSD of the API, there could be a risk of bioavailability and bio-inequivalence between batches and thus a consistent quality will not be maintained.

Follow up IR Deficiency:

FDA acknowledges your proposed three tier API particle size distribution acceptance criteria. While the numerical number (based on 3 sigma value) of the proposed limit of the API PSD is accurate, but this limit do not represent the API lots used in the clinical and registration batches as you mentioned in module 3.2.S.4.5.2.10 that, "*Particle size distributions during the clinical development using registration batches of selinexor API in the tablet core formulation (TF2), which was being scaled for commercial use, have d(10) ranging from* (b) (4) *µm and d(90) ranging from* (b) (4) *µm using the validated particle size method".* Therefore, the API lots # 1405463 and 1405531 used in your calculations were not used in any clinical trial and registration batches. Revise your API PSD acceptance criteria that reflect the PSD data used in clinical and registration batches.

Applicant's Response:
Applicant responded and confirmed that API lots # 1405463 and 1405531 were used in the clinical batches used in the clinical trial study # KCP-330003 and KCP-330-012.
Reviewer's Final Evaluation: Acceptable. The final PSD limit is:
D90-NMT (b) (4) µm, D50-NMT (b) (4) µm, and D10-NMT (b) (4) µm.

- ***DISSOLUTION ACCEPTANCE CRITERIA***

Based on the dissolution profile data of pivotal clinical batches, stability data, and manufacturing experience, the Applicant initially proposed Q= (b) (4) % at (b) (4) min, as the dissolution acceptance criterion for batch release and stability testing.

Fig.6. Dissolution Comparison of Registration (TF2.2) and Commercial-Scale Clinical Material (TF2.3) Selinexor Tablet 20 mg in the official method

Reviewer's Assessment: **ADEQUATE**

Based on the data analyses, the proposed limit (time point) appears (Q= (b)(4)% at (b)(4) minutes) to be higher than that of the observed value. Therefore, **Q= (b)(4)% in 30 minute** appears to be more appropriate. Since this drug exhibits a low solubility and high permeability, the disintegration and dissolution rate of the tablet may impact the rate of absorption and bioavailability.. The following IR comment need to be communicated to the Applicant.

IR # 2: The provided dissolution data and profile support (b)(4) dissolution acceptance criteria for your proposed product, XPOVIO™ (Selinexor) Tablets, 20 mg. Therefore, we recommend that you implement the following acceptance criteria for the dissolution test of your proposed drug product at release and on stability: Q= (b)(4)% in 30 minutes

Additionally, be advised that all proposed in process acceptance criteria; (b)(4) should meet the newly revised dissolution acceptance criteria.

Applicant's Response: The applicant has responded on 10/24/2018. Applicant has agreed on FDA's recommendation and said that they will implement the recommended dissolution acceptance criteria of Q=NLT (b)(4)% in 30 minutes. Applicant has also mentioned that the ICP limit of the tablet hardness meets the new dissolution acceptance criteria.

Reviewer's Evaluation: Acceptable with follow-up IR.

Applicant has agreed on FDA's recommended dissolution acceptance criteria. However, they have not yet updated the drug product specification in module 3.2.P.5.1.

Follow-up IR

Update you drug product specification to include the revised dissolution acceptance criteria.

Response from the Applicant: Applicant updated the specification. **Acceptable**.

- ***BIOWAIVER REQUEST:*** None
- **BRIDGING**

Effect of Formulation Change on Bioavailability: Three different formulations (2 tablet formulations[3] and 1 capsule formulation[4]), was used in a comparative bioavailability study (protocol # KCP-330-003[5]). Results showed that all different formulations were bioequivalent[6].

[3] Refer to table 7, in module 3.2.P.2

[4] Refer to table 6, in module 3.2.P.2

[5] Protocol KCP-330-003: multicenter, Phase 1b, open-label, randomized, six-arm, semi- equence- controlled crossover design study to determine the effects of food and formulation on selinexor (KPT-330) PK in male and female patients with advanced non-resectable sarcoma

Based on the result, the applicant proceeded with TF2 formulation[7] in Phase 2 and Phase 3 studies.

Bridging of Clinical product to Commercial product: The intended commercial drug product (formulation TF2.2) differs from the Phase III film-coated table (formulation TF2.3) only in color of the cosmetic film-coat. F2 similarity data between the two formulations are presented in the following table.

Table 1. F2 similarity data between the two formulations (TF2.2 – Pre change formulation and TF2.3 – post change formulation)

Compared Lots **TF2.2 : TF2.3**	(b) (4)					
L0502484 : L0607748	87	97	82	81	N/A	N/A
L0502484 : L0609209	100	83	94	90	N/A	N/A

[6] Refer to bioequivalence results (geometric mean at 90% lower and upper confidence interval) in table 13, module 3.2.P.2.

[7] Refer to table 22, in module 3.2.P.2

➢ **OVERALL BIOPHARMACEUTICS RISK ASSESSMENT: Low**

Failure mode/Risk Factor		Likelihood to impact Dissolution	Reviewer's Rational
Raw Material Attributes	API PSD	Low	Poorly soluble and highly absorbable drug. PSD variation can directly impact total surface area and thus can impact dissolution rate. (b) (4) [redacted] **Lifecycle knowledge transfer:** Although the risk of APS PSD is at low now, due to the drug's solubility nature, any change with respect to API micromeritics at post approval stage may further increase the quality risk. Therefore, any change with respect to API PSD beyond the current limit may need further clinical evaluation to assess bioavailability.
	API polymorphism	Low	(b) (4) [redacted]
	Excipient variability	Low	Effect of formulation variability showed no difference in bioavailability (Study # KCP-330-003). All three formulations (capsules, tablet TF1, and tablet TF2) are bioequivalent. Formulation differences were significant. (Ref. Table 7, 3.2.P.2)

Failure mode/Risk Factor	Likelihood to impact Dissolution	Reviewer's Rational
Manufacturing process parameters from various unit operation		(b) (4)

[8] See table 21, 22, 23, and figure 8 and 9 under Module 3.2.P.2

Failure mode/Risk Factor		Reviewer's Rational
Analytical method sensitivity /discriminating capability	Likelihood to release any defective batch by the developed dissolution method is **very low**	Dissolution method's discriminating capability was investigated and found acceptable by the reviewer. For details please see review and data in pharmaceutical development section. Appropriate statistical sampling plan from every batch is in place. (b) (4)

- **OVERALL RECOMMENDATION:**

From a Biopharmaceutics perspective, Selinexor Tablets, 20 mg, is recommended for **APPROVAL**.

Akm Khairuzzaman

Digitally signed by Akm Khairuzzaman
Date: 12/21/2018 09:02:01AM
GUID: 502d1ab500002aef5afaa6f74ddf7e69

Banu Zolnik

Digitally signed by Banu Zolnik
Date: 12/21/2018 01:23:27PM
GUID: 508da7270002a568e175a2c0dd90f334

ATTACHMENT I: Final Risk Assessment

A. Final Risk Assessment – NDA 212306

a) Drug Product: 20 mg Coated Tablet

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**
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	(b) (4)	Acceptable	Controls are in place, continue stability monitoring post approval
Physical stability (solid state)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		Acceptable	(b) (4) .
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place, continue stability monitoring post approval
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	L		Acceptable	Controls are in place, continue stability monitoring post approval
Dissolution	• Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipments • Site	M		Acceptable	Controls are in place, continue stability monitoring post approval
(b) (4)					(b) (4)

Rajiv Agarwal

Digitally signed by Rajiv Agarwal
Date: 12/13/2018 11:35:06AM
GUID: 504fa29c0000100b83d3aaa4905783c1

Anamitro Banerjee

Digitally signed by Anamitro Banerjee
Date: 12/13/2018 12:50:11PM
GUID: 5075764700003844b7bc89632228509f

Sherita McLamore

Digitally signed by Sherita McLamore
Date: 1/28/2019 02:35:46PM
GUID: 503257950000415755492db5bb8b1a5c