APPLICATION NUMBER:

212306Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
IND 114042

Karyopharm Therapeutics Inc.
Attention: Kirsten Overoye-Chan
Senior Director, Regulatory Affairs
85 Wells Avenue
Newton, MA 02459

Dear Ms. Overoye-Chan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for selinexor.

We also refer to the meeting between representatives of your firm and the FDA on June 22, 2018. The purpose of the meeting was to discuss the contents and organization of the proposed New Drug Application for selinexor.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Thomas Iype, Regulatory Project Manager, at (240) 402-6861.

Sincerely,

{See appended electronic signature page}

Vishal Bhatnagar, MD
Acting Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: June 22, 2018; 11:00 AM – 12:00 PM (EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland  20903

Application Number: IND 114042
Product Name: Selinexor, KPT-330
Indication: Selinexor, an oral XPO1 inhibitor, in combination with low-dose dexamethasone, is indicated for the treatment of patients with relapsed refractory multiple myeloma who have received at least three prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor (PI), one immunomodulatory agent (IMiD), and one anti-CD38 monoclonal antibody (mAb), and to their most recent treatment regimen.

Sponsor/Applicant Name: Karyopharm Therapeutics Inc.

Meeting Chair: Vishal Bhatnagar, MD
Meeting Recorder: Thomas Iype, PharmD, RPh

FDA ATTENDEES
Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Ann Farrell, MD, Director
Angelo de Claro, MD, Acting Deputy Director
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
Nicole Gormley, MD, Clinical Team Leader
Vishal Bhatnagar, MD, Acting Clinical Team Leader

OHOP/Division of Hematology Oncology Toxicology
Christopher Sheth, PhD, Supervisory Pharmacologist-Toxicologist

Office of Biostatistics/Division of Biometrics V
Thomas Gwise, PhD, Deputy Director
Yuan-Li Shen, DrPH, Statistical Team Leader
Qing Xu, PhD, Statistical Reviewer
Selinexor, KPT-330, is an oral XP01 inhibitor under clinical development for relapsed/refractory multiple myeloma. In the STORM (protocol KCP-330-012) study, selinexor (80 mg) was given in conjunction with low dose dexamethasone (20 mg) dosed twice weekly in 4-week cycles. The Sponsor proposes to utilize STORM as the pivotal study to support an accelerated approval. The Sponsor plans to utilize the BOSTON (protocol KCP-330-023) study as the confirmatory trial. The purpose of this meeting is to provide guidance on the content/organization of the New Drug Application (NDA) and continue discussion from the Type C meeting held between FDA and the Sponsor on January 31, 2018, concerning the integrated summary of safety and integrated summary of effectiveness to support the NDA.
2.0 DISCUSSION

Discussion following Sponsor’s presentation: The Agency clarified that use of “real-world” data (Flatiron) would require details regarding selection criteria, handling of missing data, and elimination of bias. The Agency inquired whether the Flatiron data would be used for anything other than supportive analyses. The Sponsor stated that the Flatiron data would be used for supportive analyses alone, and they would provide comprehensive selection and analysis methods for the Flatiron data.

**Question 1a:** Karyopharm is proposing updates related to the summarizing of the safety data across 8 clinical studies as 3 pools of patients. Does the Agency agree with the proposed approach and have any further comments on the ISS pooling strategy plan?

**FDA Response to Question 1a:** The pooling strategy is reasonable.

**Question 1b:** Karyopharm is proposing updates related to the summarizing of the efficacy data across Studies KCP-330-012 and KCP-330-001. Does the Agency agree with the proposed approach and have any further comments on the ISE pooling strategy plan?

**FDA Response to Question 1b:** The ISE pooling strategy is reasonable.

**Question 1c:** Karyopharm intends to present in Modules 2.7.4 and 2.7.3 the analyses of the ISS and ISE, respectively, in the same manner as described in Section V.D., Example 4 in the FDA Guidance for Industry Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document 2009.

**FDA Response to Question 1c:** Please ensure for the ISS that each pool is analyzed both individually as well as in a comprehensive fashion (i.e., combining all three pools).

**Discussion:** The Sponsor clarified that they would not combine ISS pool 3 with any other pool due to differences in data quality. The Sponsor also expressed concern that there was overlap between pool 1 and 2. The Agency understands the difficulty in combining pool 3 with pools 1 and 2 for comprehensive safety analysis. The Agency did request that the Sponsor provide an analysis combining patients from pool 1 and 2, despite potential overlap.

**Question 2:** Does the Agency agree with the described plan for reporting the PK results from Studies KCP-330-002 and KCP-330-003?

**FDA Response to Question 2:** Yes. Your plan for reporting the PK results from studies KCP-330-002 and KCP-330-003 appears acceptable. We recommend that you present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate and that the subjects’ unique ID number in the pharmacokinetic datasets is consistent with the ID numbers used in the clinical datasets.
**Discussion:** No discussion occurred.

**Question 3:** Does the Agency agree with the described plan for submission of the updated sample size reestimation, DSMB charter, and SAP to the IND for study KCP-330-023?

**FDA Response to Question 3:** Yes

**Discussion:** No discussion occurred.

**Question 4:** Does the Agency agree with the described plan to include the clinical and nonclinical ocular safety data sufficient to support the review of ocular safety in the NDA?

**FDA Response to Question 4:** The plan appears acceptable, however whether the nonclinical data sufficiently supports a review of the ocular safety in the NDA will be a review issue.

In addition to the described plan, you should include narratives for patients who have any grade visual impairment, reduced visual acuity, photopsia and cataract, which should include information on whether these ocular toxicities resolved after discontinuation of selinexor for study KCP-330-012 parts 1 and 2. You should also include narratives for all patients who have any grade 3 or 4 eye disorders, including blurred vision, across all studies that are included in the ISS pool 1 and pool 3.

**Discussion:** The Agency requested narratives for patients who have grade 3 and 4 visual adverse events, regardless of whether they were categorized as serious adverse events. The sponsor agreed to provide these narratives, regardless of investigator attribution.

**Question 5:** Does the Agency agree that the nonclinical ADME, toxicology, and safety pharmacology studies conducted to date are sufficient for filing and Agency review of the NDA?

**FDA Response to Question 5:** The nonclinical pharmacology and toxicology package with selinexor (KPT-330) as described in the meeting briefing document appears sufficient to file the NDA.

**Discussion:** No discussion occurred.

**Question 6:** Does the Agency agree with the proposed plan for assessing the population PK and exposure-response analyses for the NDA?

**FDA Response to Question 6:** Yes. Your proposed plan for assessing the population PK and exposure-response analyses appear acceptable; however, we do not agree that you can adequately assess the effect of organ impairment on the pharmacokinetics of selinexor based
on the restricted eligibility criteria for the patients whose data will be used in the modeling. See response to Question 7 regarding the need for organ impairment study.

**Discussion:** No discussion occurred.

**Question 7:** Does the Agency agree that the in vitro and in vivo metabolism profile and overall clinical pharmacology program described above is acceptable for NDA submission?

**FDA Response to Question 7:** No. As selinexor is excreted primarily by hepatobiliary route into feces, you should investigate the impact of hepatic impairment on the PK of selinexor in human; however, your proposed population PK analysis is not expected to provide a sufficient assessment of the effects of hepatic impairment on the pharmacokinetics of selinexor and identify an appropriate dose in patients with moderate or severe hepatic impairment, since your completed and ongoing clinical trials only included patients with mild hepatic impairment and part of patients with moderate hepatic impairment (total bilirubin < 2 x ULN). Therefore, you should conduct a dedicated hepatic impairment study prior to NDA submission. Please refer to the [FDA guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling](https://www.fda.gov/Drugs/Guidances/default.htm) for more information.

Since the fraction of dose excreted unchanged selinexor in the urine is unclear in human based on the limited information provided in the meeting package, and your completed and ongoing clinical trials excluded part of patients with severe renal impairment (estimated creatinine clearance < 20 mL/min).

In addition, as selinexor is a substrate of multiple UGT isoforms and CYP3A4, you should conduct clinical drug interaction studies to assess the impact of inhibitors and inducers of CYP3A4 on the PK of selinexor prior to NDA submission.

Moreover, the in vitro study showed that selinexor had an inhibitory effect on human CYP3A4 with an IC₅₀ of 4.7 μM. Therefore, selinexor is a potential inhibitor of CYP3A4/5 with a R₁ of 1.03 in human at the clinically relevant maximum concentration (Cₜₐₓ) of 542 ± 124.8 ng/mL (1.2 ± 0.28 μM) at the proposed dose regimen of 80 mg BIW.

**Discussion:** The proposed plan to assess the effect of baseline hepatic impairment on selinexor PK via population PK analysis with data from only two patients with severe hepatic impairment is not sufficient. Therefore, a dedicated hepatic impairment study is recommended to be conducted prior to NDA submission. It is FDA’s expectation that...
the NDA submission should be complete at the time of NDA submission. For clinical pharmacology studies that cannot be completed prior to the NDA submission, appropriate restrictions should be included in the proposed labeling and post marketing requirements will be requested. Karyopharm commits to conducting a dedicated PK study to assess the effect of hepatic impairment on the PK of selinexor.

Karyopharm clarified that there is data on 15 patients with baseline severe renal impairment. The adequacy of Karyopharm’s proposal to evaluate the effect of renal impairment on selinexor PK via population PK analysis will be reviewed during the NDA submission.

The FDA guidance states that an in-vivo study should be conducted if glucuronidation or CYP enzyme metabolism account for greater than 25% of total metabolism. It is FDA’s expectation that the NDA submission should be complete at the time of NDA submission. For clinical pharmacology studies that cannot be completed prior to the NDA submission, Karyopharm will submit additional data analysis to support the need for clinical drug-drug interaction studies.

**Question 8:** Does the agency agree with the suggested integrated approach of intensive ECG data acquisition in an early phase dose escalation study, utilization of exposure-QTc analysis and clinical evaluation of supratherapeutic dose and that thorough QT study is not required for NDA submission?

**FDA Response to Question 8:** The Sponsor’s submitted information is insufficient to comment about the adequacy of data to characterize QTc prolongation potential and to exclude the large mean QTc effects (20 ms) at the therapeutic dose. We recommend that the sponsor provide the ECG/PK assessment schedule, sample size for each dose level, ECG acquisition/measurement methodology, ECG analysis plan and the highlights of clinical pharmacology table in order to evaluate the adequacy of proposed approach by the Sponsor.

**Discussion:** The sponsor has provided additional details of their plan in their response. The interpretation of sponsor’s data for QTc prolongation would be a review issue and we have the following recommendations for the sponsor for their NDA submission:

i) For the analysis and reporting of results for concentration-QTc (exposure-response) analysis, follow the recommendations described in “Scientific white paper on concentration-QTc modeling” (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2017; doi 10.1007/s10928-017-9558-5) and “Correction to: Scientific white paper on concentration-QTc modeling” (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2018; doi 10.1007/s10928-017-9565-6).

ii) Provide by-time central tendency analysis and standard categorical outlier analyses for ECG intervals.

**Question 9:** Understanding that labeling is a review issue, does the Agency have any initial comments or concerns on the overall structure, format, and initial outline of the label information?
**FDA Response to Question 9:** It is premature to discuss labeling at this time, as the Agency has not reviewed safety and efficacy data. We refer you to the Guidance “Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements” for formatting and structural considerations. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075082.pdf.

We recommend the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application be consistent with FDA Guidance for Industry, “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format.” Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the guidance.

**Discussion:** No discussion occurred.

**Question 10:** Does the Agency agree with Karyopharm’s proposal for the 120-day (or 90-day, if priority review is granted) update?

**FDA Response to Question 10:** No, we do not agree with the submission of clinical pharmacology study reports with the 120- or 90-day Safety Update. Refer to Question 7.

You should clarify the data cutoff date for the 120- or 90-day Safety Update.

**Discussion:** No discussion occurred.

**Question 11:** Does the Agency agree with Karyopharm’s plan to provide financial disclosure for covered studies KCP-330-001 and KCP-330-012 in section 1.3.4 of the NDA?

**FDA Response to Question 11:** No, you should provide financial disclosure information for all investigators from KCP-330-001 and KCP-330-012 (Parts 1 and 2). Refer to “Guidance for Clinical Investigators, Industry, and FDA Staff – Financial Disclosure by Clinical Investigators”, available at the following link: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afdag-gen/documents/document/ucm341008.pdf.

**Discussion:** No discussion occurred.

**Question 12:** Does the Agency agree with the plan for rolling submission of the initial NDA?

**FDA Response to Question 12:** See the responses to questions 10 and 7. In addition, please provide your projected timeline of the planned rolling NDA submission, broken down by modules and expected submission dates. Also, refer to the Discussion Of The Content Of A Complete Application under Other Important Information (section 3.0) below. The review clock begins at the time of the final submission.
Discussion: No discussion occurred.

Question 13: Does the Agency agree with the proposed Table of Contents for the NDA in eCTD format?


Additionally, the Office of Scientific Investigations (OSI) is piloting a risk based model for clinical inspection site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft, “Bioresearch Monitoring Technical Conformance Guide - Summary Level Clinical Site Data for CDER’s Inspection Planning”, available at the following link: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf for the structure and format of this data set.

Finally, be sure that you include the clinical protocols for each study along with version history and investigator list.

Discussion: No discussion occurred.

Additional Clinical Comment:

For studies KCP-330-001 and KCP-330-012, you should include clinical narratives (not only CRFs) for patients who have (1) death within 30 days of the last dose of any study treatment, (2) discontinuation of study treatment due to treatment emergent AE, (3) treatment emergent serious AEs, (4) the visual AEs as described in the response to Question 4, (5) treatment emergent tumor lysis syndrome grade 3 or higher, (6) treatment emergent hemorrhage events (SAEs or grade 3 or higher), (7) treatment emergent hyponatremia grade 3 or higher. These narratives should include information on the timing, severity, action taken by the clinical staff, and outcome of the adverse event in relation to study drug. Be advised that the above narratives should be submitted irrespective of investigator or company attribution of relatedness to study drug.

Additional Clinical Pharmacology Comments:

1) Address the following questions in the Summary of Clinical Pharmacology:
   a. What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application? Include justification for the targeted percent inhibition of XPO1 mediated nuclear export and targeted occupancy. Identify
individuals who required dose modifications, and provide time to the first dose
modification and reasons for the dose modifications in support of the proposed dose
and administration.

b. What are the exposure-response relationships for efficacy, safety and biomarkers?
c. What is the effect of selinexor on the QT/QTc interval?
d. What are the characteristics of absorption, distribution, and elimination (metabolism
and excretion)?
e. What are the effects of food on the bioavailability? What are the dosing
recommendations with regard to meals or meal types? Provide justification for
recommendation with regard to meals or meal types.
f. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex,
race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What
dose modifications are recommended?

2) Apply the following advice in preparing the clinical pharmacology sections of the
original submission:

a. Provide the final study report for all in vitro studies that assessed the potential for an
interaction of selinexor with drug metabolizing enzymes and transporters in humans.
Provide justification for not conducting clinical trials to further evaluate these
interactions.
b. Submit bioanalytical methods and validation reports for all clinical pharmacology and
biopharmaceutics trials.
c. Provide final study report for each clinical pharmacology trial. Present the
pharmacokinetic parameter data as geometric mean with coefficient of variation (and
mean ± standard deviation) and median with minimum and maximum values as
appropriate.
d. Provide complete datasets for clinical pharmacology and biopharmaceutics trials.
The subjects’ unique ID number in the pharmacokinetic datasets should be consistent
with the numbers used in the clinical datasets.
  • Provide all concentration-time and derived pharmacokinetic parameter datasets as
    SAS transport files (*.xpt). A description of each data item should be provided in
    a define.pdf file. Any concentrations or subjects that have been excluded from
    the analysis should be flagged and maintained in the datasets.
  • Identify individual subjects with dose modifications; the time to the first dose
    reduction, interruption or discontinuation; the reasons for dose modifications in
    the datasets.
e. Submit the following for the population pharmacokinetic analysis reports:
  • Standard model diagnostic plots
  • Individual plots for a representative number of subjects. Each individual plot
    should include observed concentrations, the individual prediction line and the
    population prediction line
  • Model parameter names and units in tables.
  • Summary of the report describing the clinical application of modeling results.
Refer to the following pharmacometric data and models submission guidelines

f. Submit the following information and data to support the population pharmacokinetic analysis:
   • SAS transport files (*.xpt) for all datasets used for model development and validation
   • A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
   • Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)

3) Include the following items when you submit your QT study report:
   a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
   b. Electronic copy of the study report
   c. Electronic or hard copy of the clinical protocol
   d. Electronic or hard copy of the Investigator’s Brochure
   e. Annotated CRF
   f. A data definition file which describes the contents of the electronic data sets
   g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
   h. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
   i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
   j. Narrative summaries and case report forms for any:
      • Deaths
      • Serious adverse events
• Episodes of ventricular tachycardia or fibrillation
• Episodes of syncope
• Episodes of seizure
• Adverse events resulting in the subject discontinuing from the study
• ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
• A completed Highlights of Clinical Pharmacology Table

Advancing in this field – and possibly reducing the burden of conducting QT studies –
depends critically upon obtaining the most comprehensive understanding of existing data.
Please consider making your data, at least placebo and positive control data, available for
further research purposes; see, for examples, the Data Request Letter at http://cardiac-
safety.org/ecg-database/.

Additional Statistical Comments:

1) FDA requests that an Analysis Data Reviewer’s Guide (ADRG) and Study Data
Reviewer’s Guide (SDRG), an important part of a standards-compliant study and analysis
data submission, be prepared and submitted in the NDA. Please refer to the “Study Data

2) Provide sufficient comments, adequate bookmarks, and hyperlinks in the define file(s) to
ensure efficient review.

3) Provide executable SAS program(s) with adequate document(s) to allow FDA to
duplicate the analysis datasets derivation from raw datasets

4) Provide the SAS programs as well as format library files used for efficacy and safety data
analysis. If the SAS programs use any SAS macro, please provide all necessary macro
programs.

5) The Agency requests the Sponsor also submit the raw data from which the analysis data
were derived. In addition, the Sponsor must also submit code that was used to transform
the raw data to the key efficacy and safety analysis data.

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

• The content of a complete application was discussed. Please refer to the “Discussion”
sections above.

• All applications are expected to include a comprehensive and readily located list of all
clinical sites and manufacturing facilities included or referenced in the application.

• Major components of the application are expected to be submitted with the original
application and are not subject to agreement for late submission. You stated you intend
to submit a complete application and therefore, there are no agreements for late submission of application components.

**PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that marketing applications for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020 contain reports of molecularly targeted pediatric cancer investigations. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf). In addition, you may contact the Division of Pediatric and Maternal Health at
301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to:

**SUBMISSION FORMAT REQUIREMENTS**

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. The following submission types: NDA, ANDA, BLA, **Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ctd.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification for Transmitting Electronic Submissions using eCTD Specifications. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

To facilitate our inspensional process, we request that you clearly identify in a single location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”
### OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:


PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug’s use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion at this time.
5.0 ACTION ITEMS

There are no action items.

6.0 ATTACHMENTS AND HANDOUTS

We make reference to your email communication on June 20, 2018, containing a presentation titled “Karyopharm Therapeutics-Opening Remarks-Dr. Michael Kauffman-June 22, 2018”.

We also make reference to your email communication on June 14, 2018, containing a document titled “Response to FDA Pre-NDA Meeting Preliminary Comments Selinexor-Selinexor Pre-NDA Meeting – 22 June 2018”.

64 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VISHAL BHATNAGAR
07/02/2018
IND 114042

Karyopharm Therapeutics
Attention: Kirsten Overoye-Chan
Senior Director, Regulatory Affairs
85 Wells Ave.
Newton, MA  02459

Dear Ms. Overoye-Chan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for selinexor.

We also refer to the meeting between representatives of your firm and the FDA on July 25, 2016. The purpose of the meeting was to discuss (b) (4)

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Theresa Carioti, Chief, Regulatory Project Management at (301) 796- 2848.

Sincerely,

{See appended electronic signature page}

Nicole Gormley, MD
Acting Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

28 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NICOLE J GORMLEY
08/08/2016