CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761148Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 103461

MEETING MINUTES

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, RAC
Vice President, Global Regulatory Affairs
157 Technology Drive
Irvine, CA 92618

Dear Mr. Hiteshi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SPI-2012.

We also refer to the meeting between representatives of your firm and the FDA on August 21, 2018. The purpose of the meeting was to discuss the efficacy and safety data, proposed indication as well as structure and content of your proposed marketing application for eflapegrastim.

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 Rachel McMullen, Senior Regulatory Project Manager at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-BLA
Meeting Date and Time:	August 21, 2018; 1:00-2:00PM (ET).
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1311 Silver Spring, Maryland 20903
Application Number:	IND 103461
Product Name:	SPI-2012 (Rolontis)
Indication:	(b) (4)
Sponsor/Applicant Name:	Spectrum Pharmaceuticals, Inc.
Meeting Chair:	Tanya Wroblewski, MD, Acting Clinical Team Leader
Meeting Recorder:	Rachel McMullen, MPH, MHA, Senior Regulatory Project Manager

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Albert Deisseroth, MD, PhD, Supervisory Associate Deputy Director
Nicole Gormley, MD, Deputy Director (Acting)
Tanya Wroblewski, MD, Acting Clinical Team Leader
Rosanna Setse, MD, Medical Officer
Rachel McMullen, MPH, MHA, Senior Regulatory Project Manager

Office of Biostatistics/Division of Biometrics V
Jingjing Ye, PhD, Statistical Team Leader
Yeh Fong Chen, Statistical Team Leader
Kate Dwyer, PhD, Statistical Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Olanrewaju Okusanya, Pharm D, MS, Clinical Pharmacology Team Leader
Vicky Hsu, PhD, Clinical Pharmacology Reviewer

Office of Biotechnology Products
Rachel Novak, PhD, Product Quality Team Leader

EASTERN RESEARCH GROUP ATTENDEES
Marc Goldstein, Independent Assessor
Kuang-Heng Hsaio, Independent Assessor

SPONSOR ATTENDEES
Spectrum Pharmaceuticals Inc.
Thomas Riga, Chief Operating Officer
Zane Yang, MD, Senior Vice President - Clinical Development
Gajanan Bhat, PhD, Vice President, Biostatistics, Data Management, Medical Writing
Guru Reddy, PhD, Vice President, Preclinical Research
Shanta Chawla, MD, Executive Director, Clinical Development
Prasad Kolli, PhD, Director, R&D Biologics
Anil K. Hiteshi, RAC, Vice President, Global Regulatory Affairs, Pharmacovigilance, and Clinical Document Management

Consultant to Spectrum
(b) (4)

1.0 BACKGROUND

Spectrum Pharmaceuticals is developing eflapegrastim (SPI-2012, HM10460A, Rolontis), which is a long-acting recombinant human granulocyte colony-stimulating factor (rh-G-CSF). The proposed indication is to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

This application does not have orphan designation and no pediatric studies have been conducted to date. Per the Agency's written response letter dated July 17, 2018, the Sponsor plans to submit an agreed iPSP.

The Sponsor also submitted a request for waiver of the Human Factors study on April 30, 2018.

On June 18, 2018, Spectrum requested a pre-BLA meeting to discuss the efficacy and safety data, proposed indication as well as the structure and content of the proposed marketing application. The Sponsor plans to request a separate CMC specific pre-BLA meeting. The Sponsor anticipates submission of this 351(a) marketing application in December 2018.

FDA sent Preliminary Comments to Spectrum on August 14, 2018.

2. DISCUSSION

Clinical Questions

Question 1 - BLA Efficacy Data
The Sponsor believes the data from the SPI-GCF-301 and SPI-GCF-302 Phase 3 studies having individually met their primary endpoints, provide the substantial evidence of efficacy to support the filing of the eflapegrastim BLA. Does the Agency agree?

FDA RESPONSE: The topline efficacy data you provided in the meeting package appears to demonstrate non-inferiority of eflapegrastim to pegfilgrastim; however, the Agency cannot concur with your conclusions until we conduct our own independent analysis of the datasets to confirm the efficacy claims.

Meeting Discussion: There was no discussion.

Question 2 – Safety and Immunogenicity Data
The Sponsor believes that the proposed safety and immunogenicity package is sufficient for the BLA filing. Does the Agency agree?

FDA RESPONSE: Your proposal appears reasonable. Ultimately the adequacy of your safety data will be a review issue.

Similar G-CSF products are noted to have adverse reactions of capillary leak syndrome, severe allergic reactions, complications with sickle cell disease, acute respiratory distress syndrome (ARDS) and splenic rupture. Include a discussion of these potential adverse reactions in relation to your product in your application.

With the class of G-CSF growth factor drugs there is a potential for tumor growth stimulatory effects on malignant cells as malignant cell lines possess GCSF receptors on their cell surface raising theoretical concern that your product and related products may promote neoplastic cell growth. Please provide a discussion of this theoretical risk and your agent in the application.

Include safety narrative summaries of important adverse events (AEs) (e.g., deaths, events leading to discontinuation, other SAEs) that provide the detail necessary to permit an adequate understanding of the nature of the adverse event experienced by the study subject.

We agree with your plan to submit complete 9-month follow up safety data for Study SPI-GCF-302 with the 120-day safety update, and the 12-month follow-up data in August 2019.

To support the meaningfulness of the clinical ADA data, the BLA submission must include method validation protocols and reports for the immunogenicity assays that were used to analyze the clinical samples. The adequacy of the immunogenicity assays will be a review issue. Based on the information provided in the meeting package, we disagree with your sample analysis scheme for detecting and characterizing binding ADAs (Section 11.3.5.1.2.4). In addition to the

proposed domain specificity testing outlined in Figure 5, samples that confirm positive for ADAs to eflapegrastim in the confirmatory assay should be evaluated for ADA cross-reactivity to endogenous human G-CSF. Confirmed positive samples that have ADA responses specific to the G-CSF moiety of eflapegrastim and ADA responses that are cross-reactive to endogenous human G-CSF should be evaluated for neutralizing antibodies.

You should also evaluate the impact of immunogenicity on eflapegrastim PK, in addition to its impact on PD, safety/tolerability, and efficacy. For the evaluation of the ADA impact on PK, we recommend that you include between-subject comparison (i.e., between ADA positive subjects and ADA negative subjects) as well as within-subject comparison (i.e., before ADA positive and after ADA positive) of PK data. We encourage you to include subjects ADA status as a covariate in the population PK analysis on an exploratory basis to evaluate the impact of ADA on PK of your drug. In the population PK analysis, further explore the necessity of treating the subject ADA status as a time-varying variable for ADA positive subjects with or without the ADA titer data.

Meeting Discussion: There was no discussion.

Question 3 – Indication for Eflapegrastim
Does the Agency agree that the proposed indication is acceptable?

FDA RESPONSE: The proposed indication is a good starting point. Final negotiation and determination of the proposed indication is made during the review of the application.

Meeting Discussion: There was no discussion.

Question 4 – ISE and ISS
Does the Agency agree with the plan for the preparation of the ISE and the ISS?

FDA RESPONSE: Yes. Your proposed plan for ISE and ISS is acceptable.

Meeting Discussion: There was no discussion.

Question 5 – Population Pharmacokinetics and Pharmacokinetic/Pharmacodynamic Analysis
Does the Agency agree with our proposed plan of population PK for exposure-response analysis and PK/PD data analysis for cardiac safety?

FDA RESPONSE: Yes, we agree with your proposed plan of exposure-response analysis for cardiac safety. In addition to your exposure-response analysis for cardiac safety using data collected in study SPI-GCF-301-PK, please submit your categorical analysis, outlier analysis, and morphological analysis for review.

Your proposed plan of population PK and exposure-response analysis appear acceptable. Since the clearance of eflapegrastim is potentially mediated by neutrophil (similar to filgrastim and pegfilgrastim), we encourage you to consider a PD-mediated drug disposition model for

characterizing the PK and PD (ANC) profiles of eflapegrastim. Refer to additional clinical pharmacology comments regarding our general expectations for your BLA submission.

Meeting Discussion: There was no discussion.

Statistical Question

Question 6 – Statistical Datasets
Does the Agency agree with the plan and format of the submission data?

FDA RESPONSE: Please ensure compliance with the latest version of the STUDY DATA TECHNICAL CONFORMANCE GUIDE: Technical Specifications Document (March, 2018) https://www.fda.gov/downloads/forindustry/datastandards/studydatastandards/ucm384744.pdf

Please also provide the following:

- ADAM datasets and the corresponding DEFINE files for the pivotal studies SPI-GCF-301 and SPI-GCF-302, ISE, and ISS. Please also provide define files in pdf format and submit all programs involving the creation of these derived datasets.
- Readable, clearly commented, non-macro programs in ASCII format used to create tables and figures for your primary and key secondary efficacy analyses and any additional information included in Section 14 CLINICAL STUDIES of the Prescribing Information, if applicable. Ensure these programs call only data submitted to the Agency and can be easily used to reproduce the results in the CSR.
- A clear index with descriptions of the programs.
- Annotations for each figure and table in the CSR with a link to the program used to generate results.

Meeting Discussion: There was no discussion.

BLA Content and Structure Question

Question 7 – eCTD Table of Contents
Does the Agency have any additional suggestions regarding the proposed organization of the 351(a) BLA submission?

FDA RESPONSE: From a technical standpoint (not content related), the proposed organization of the planned BLA is acceptable.

Meeting Discussion: There was no discussion.

Additional Clinical Pharmacology Comments
Address the following questions in the Summary of Clinical Pharmacology:

1. What is the basis for dose selection in the following stages of drug development: first-in-human starting dose, dose range in phase 1 and phase 2 studies, the dose(s) in registration

trials and the final proposed dose(s) to support your marketing application? 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.
2. What are the exposure-response relationships for efficacy, safety, and biomarkers?
3. How do extrinsic (e.g., other drugs) and intrinsic factors (e.g., sex, race, body weight, organ dysfunctions, and disease) influence the exposure, efficacy, or safety of your drug? What dose modifications are recommended?
4. What is the impact of immunogenicity on exposure, efficacy, and safety?

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

1. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
2. 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 range as appropriate.
3. 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.
4. 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 http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.
5. 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)

6. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf for population PK http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for exposure-response relationships, and http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm for pharmacometric data and models submission guidelines.
7. We recommend that 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" (available at https://go.usa.gov/xn4qB). 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 above guidance.

8. When you submit your study report for cardiac safety, please include the following items:
    - Study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
    - Study report
    - Statistical analysis plan
    - Clinical study protocol
    - Investigator's Brochure
    - A completed Highlights of Clinical Pharmacology and Cardiac Safety Table
    - Annotated CRF
    - A data definition file which describes the contents of the electronic data sets
    - Electronic data sets as SAS.xpt transport files (in CDISC SDTM and ADAM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses. Please make sure that the ECG raw data set includes at least the following: Subject ID, treatment, period, ECG date, ECG time (down to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (including any corrected QT, e.g., QTcB, QTcF, QTcN, QTcI, along with the correction factors for QTcN and QTcI), Lead, and ECG ID (link to waveform files, if applicable).
    - Data set whose QT/QTc values are the average of the above replicates at each nominal time point
    - Adverse Event analysis using the MedDRA SMQ "Torsade de pointes/QT Prolongation" and include the preferred term "Seizure" by treatment and dose level.
    - 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

9. Submit all related ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)

Meeting Discussion: There was no discussion.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The content of a complete application was discussed.

The Sponsor clarified that they will submit all the validation assays for immunogenicity at the time of the BLA submission.

The Sponsor will provide immunogenicity data for approximately 195 patients at the time of the BLA submission and will provide 12 month follow-up immunogenicity data for approximately 50 patients within 30 days of receipt of the BLA. The Sponsor stated that they will also update the immunogenicity assessment as it relates to the PK of eflapegrastim and will provide an update to the Agency within 30 days. This proposal is acceptable to the Agency and is considered a minor component.

The Agency recommends that for Module 3 the Sponsor have individual folders for the different drug substance intermediates.

The Agency agrees with submission of the risk management plan (RMP) in Module 1.16 of the BLA submission; however the determination of the need for a REMS is made during the review of the application.

- 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.

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan..

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:

    1. **The Sponsor will provide 12 month follow-up immunogenicity data for approximately 50 patients within 30 days of receipt of the BLA. The Sponsor will provide immunogenicity data for approximately 195 patients at time of BLA submission.**

2. **The Sponsor stated that they will update the immunogenicity assessment as it relates to the PK of eflapegrastim and will provide an update to the Agency within 30 days.**

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

BLA NUMBER: LATE COMPONENT - BIOMETRICS
BLA NUMBER: LATE COMPONENT - CLINICAL
BLA NUMBER: LATE COMPONENT - CLINICAL PHARMACOLOGY
BLA NUMBER: LATE COMPONENT - NONCLINICAL
BLA NUMBER: LATE COMPONENT - QUALITY

In addition, we note that a chemistry pre-submission meeting is planned. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (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, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies 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. 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: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

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.

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/ectd.

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 *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

MANUFACTURING FACILITIES

To facilitate our inspectional 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."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

A copy of the Sponsor's presentation materials is attached for reference.

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

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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/

TANYA M WROBLEWSKI
08/23/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 103461

MEETING MINUTES

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, RAC
Vice President, Global Regulatory Affairs
157 Technology Drive
Irvine, CA 92618

Dear Mr. Hiteshi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SPI-2012.

We also refer to the meeting between representatives of your firm and the FDA on Friday, December 12, 2014. The purpose of the meeting was to discuss further clinical development of SPI-2012.

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 Rachel McMullen, Regulatory Project Manager at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	Friday, December 12, 2014; 9:00AM - 10:00AM EST
Meeting Location:	FDA White Oak Federal Research Center 10903 New Hampshire Avenue White Oak Bldg 22, Room 1315 Silver Spring, MD 20903
Application Number:	IND 103461
Product Name:	SPI-2012
Proposed Indication:	[redacted] (b) (4) incidence of infection, as manifested by febrile neutropenia in patients with [redacted] (b) (4) non-myeloid malignancies receiving myelosuppressive anti-cancer [redacted] (b) (4)
Sponsor/Applicant Name:	Spectrum Pharmaceuticals, Inc.
Meeting Chair:	Albert Deisseroth, MD, PhD; Clinical Team Leader
Meeting Recorder:	Rachel McMullen, MPH; Regulatory Project Manager

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products:
Albert Deisseroth, MD, PhD, Clinical Team Leader
Donna Przepiorka, MD, PhD, Clinical Reviewer
Rachel McMullen, MPH, Regulatory Project Manager

OHOP/Division of Hematology, Oncology, Toxicology
Haw-Jyh Chiu, PhD, Acting Team Leader
Christopher Sheth, PhD, Pharmacologist

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Brian Booth, PhD, Deputy Director
Bahru Habtemariam, PhD, Acting Team Leader

Office of Biostatistics/Division of Biometrics V
Lei Nie, PhD, Team Leader

SPONSOR ATTENDEES

Rajesh C. Shrotriya, MD, Chairman and Chief Executive Officer
Lee F. Allen, MD, PhD, Chief Medical Officer
Guru Reddy, PhD, Vice President, Preclinical Research and Development
Gajanan Bhat, PhD, Vice President, Biostatistics, Data Management, Medical Writing
Mi Rim Choi, MD, Medical Director, Clinical Development
Prasad Kolli, PhD, Director, Research and Development, Biologics
Anil K. Hiteshi, RAC, Vice President, Global Regulatory Affairs
(b) (4)

1.0 BACKGROUND

On September 25, 2014, Spectrum Pharmaceuticals, Inc. requested an End of Phase 2 meeting to discuss further clinical development of SPI-2012. SPI-2012 is a novel biologic, which is the conjugate of a modified rh-G-CSF (HM10411) and human IgG4 Fc fragment (HMC001) *via* two chemical bonds between an amino group of the N-terminus of each protein and polyethylene glycol dialdehyde. The proposed indication for use is (b) (4) in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer therapy.

The Sponsor has proposed two multi-center, randomized, active-controlled studies for the Phase 3 development program to support the Biologic License Application (BLA). These studies are as follows: a Phase 3 Breast Cancer Study-SPI-GCF-301 and a Phase 3 Non-Hodgkin's Lymphoma Study-SPI-GCF-302. Spectrum Pharmaceuticals Inc. has requested this meeting to obtain agreement on the design of the Phase 3 studies that will support the BLA for SPI-2012.

On December 9, 2014, FDA provided the sponsor with preliminary meeting responses to the questions contained in the November 12, 2014 meeting package.

2.0 DISCUSSION

2.1 NON-CLINICAL QUESTIONS:

Question 1-Non-Clinical Safety Assessment

a. *Spectrum conducted embryo-fetal toxicity studies in two species. Because SPI-2012 is indicated for the treatment of patients with advanced cancer, Spectrum believes that no further reproductive toxicology studies are required. Does the Agency agree?*
b. *SPI-2012 is not mutagenic and it is indicated for the treatment of patients with advanced cancer. Therefore, Spectrum believes that carcinogenicity studies are not required. Does the Agency agree?*

c. *Spectrum believes that the existing non-clinical safety assessment package is adequate for the initiation of Phase 3 studies and to support the review of the planned BLA for SPI-2012. Does the Agency agree?*

FDA Response:
The types of non-clinical studies referred to in Tables 1 and 2 of your background material are sufficient to support initiation of Phase 3 clinical trials of SPI-2012 and BLA submission, however any final determination on the adequacy of the data and the potential need for additional non-clinical studies will be made during our review.

DISCUSSION:
There was no discussion.

2.2 CLINICAL QUESTIONS:

Question 2- Acceptability of the Two Proposed Phase 3 Studies

a. *Does the Agency agree that the two proposed multi-center, randomized, active-controlled Phase 3 studies, as described below, are acceptable and will provide sufficient data to support the review of the SPI-2012 BLA for the following proposed indication?*
   - [redacted (b) (4)] *incidence of infection, as manifested by febrile neutropenia, in patients with* [redacted (b) (4)] *non-myeloid malignancies receiving myelosuppressive anti-cancer therapy.*

FDA Response:
No. See responses below. Please also clarify where the trials will be conducted (US or ex-US) and what is the source of the pegfilgrastim that will be used in the trials.

DISCUSSION:
The Sponsor explained that the trial will be global and the intention is to use US licensed Neulasta at US sites [redacted (b) (4)] ***the comparator. FDA explained*** [redacted (b) (4)] ***The Sponsor is also considering*** [redacted (b) (4)] ***The Agency strongly recommended*** [redacted (b) (4)]

b. *Does the Agency agree with the design of the proposed multi-center, randomized, active-controlled Phase 3 study in patients with breast cancer receiving TC therapy?*

FDA Response:
No. As per our correspondence on November 16, 2012, the trial should be designed using a 0.6 day margin versus US-licensed Neulasta.

DISCUSSION:
See discussion below.

c. *Does the Agency agree with the design of the proposed* [redacted] (b) (4)

FDA Response: No.

[redacted] (b) (4)

DISCUSSION:
The Agency pointed out that [redacted] (b) (4) ***The Agency also explained that the 0.62 day margin would apply to this population.***

The Sponsor inquired as to whether [redacted] (b) (4)

Clinical trials involving only a breast cancer, have led to approval of a long acting filgrastim product.

Question 3- Primary Endpoint: Duration of Severe Neutropenia
Does the Agency agree with the proposed primary endpoint of Duration of Severe Neutropenia (DSN), its definition and the focus on the measurement of DSN in Cycle 1 of the two planned Phase 3 Studies?

FDA RESPONSE: Yes

DISCUSSION:
There was no discussion.

Question 4 - Secondary Endpoints
Does the Agency agree with the proposed list of secondary endpoints for the two planned Phase 3 studies?

FDA Response: Yes

DISCUSSION:
There was no discussion.

Question 5- Dosing
Does the Agency agree with the proposed fixed dose of SPI-2012 to be used for the two planned Phase 3 studies?

FDA Response:
Your proposed fixed dose appears acceptable. However, we recommend you evaluate two dose levels in your phase 3 trials.

DISCUSSION:
The Agency recommended that the Sponsor conduct pharmacokinetics pharmacodynamics (pk pd) simulations to explore the impact of conversion to fixed dose regimen on the exposure and absolute neutrophil count (ANC) profile of the product. The Sponsor agreed to conduct the recommended simulations and to get back to the Agency. The two dose proposal is a recommendation, not a requirement.

Question 6-Statistical Methods and Sample Size
a. Does the Agency agree with the planned statistical methods of analysis and sample size determination for the two proposed Phase 3 randomized studies?
b. Does the Agency agree with the proposed Type I Error control strategy?

FDA Response:
No. The sample size should be calculated based on a non-inferiority margin of 0.6 days. In addition, please provide justification including simulations to demonstrate that the bootstrap resample method is a valid method for construction of confidence intervals with the target sample size, using assumptions that are reasonable for the primary endpoint. You may generate simulation datasets based on your Phase 2 data. We also recommend that you compare performance of different methods including the bootstrap resample method, t-test, and Poisson regression model using the same simulation datasets.

A formal statistical analysis plan (SAP) should be submitted for review before the start of these open-label trials. If the bootstrap resample method will be used either as a primary analysis or a sensitivity analysis, please provide the detailed program code in the SAP including the specific resampling methods and the seed generating the random variables.

We agree that a hierarchical testing procedure controls the type I error rate, but we recommend that you provide details in your SAP.

We will provide additional comments, as needed, after reviewing your protocol and SAP.

DISCUSSION:
The Agency explained how the margin was derived and why it is necessary to prevent biocreep. The Agency recommends a two-sided 90%confidence interval to make the comparison. The Agency also recommended that the Sponsor provide a more detailed protocol document which incorporates not only the 90% confidence intervals but other design features which will ensure full characterization of the study population at baseline with respect to prognosis and a longer term follow up for safety.

Postmeeting Note: The Agency wishes to clarify that the two-sided 90% confidence interval could be used only for a candidate biosimilar product. Since SPI-2012 is a new molecular entity, the pivotal trial should employ the usual noninferiority design with a 95% confidence interval. For additional information please see "Guidance for Industry Non-Inferiority Clinical Trials" available at: http://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf.

3.0 OTHER IMPORTANT MEETING INFORMATION:

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies 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 PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP 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. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items 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 field investigators who conduct those inspections (Item I and II). 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.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

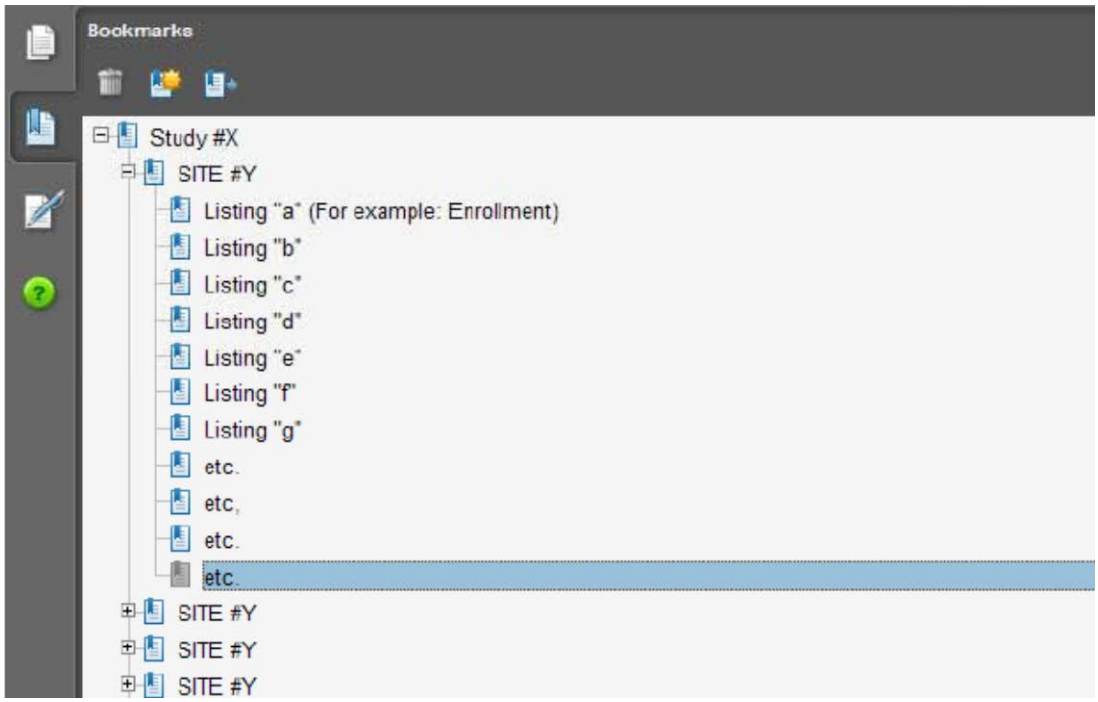
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
    a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
    b. Subject listing for treatment assignment (randomization)
    c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
    d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
    e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
    f. By subject listing, of AEs, SAEs, deaths and dates
    g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
    h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
    i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
    j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

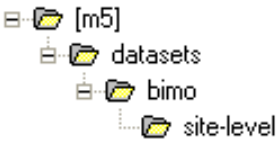
OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry *Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning*" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

No action items were identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor responses to FDA preliminary comments are attached.

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

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

/s/

ALBERT B DEISSEROTH
12/19/2014