CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761166Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 119047

MEETING MINUTES

PharmaEssentia Corporation
C/o PharmaEssentia US, LLC
Attention: Craig Zimmerman, PhD
Vice President, Medical and Drug Development
35 Corporate Drive, Suite 325
Burlington, MA 01803

Dear Dr. Zimmerman:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ropeginterferon-*a*-2b solution for injection (P1101).

We also refer to the meeting between representatives of your firm and the FDA on September 4, 2019. The purpose of the meeting was to discuss the proposed format and the adequacy of the available regulatory, clinical, non-clinical, and biostatistics issues to support the filing of a proposed BLA for your drug product and its marketing approval in the United States.

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}

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

Enclosure:

- Meeting Minutes

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: September 4, 2019; 1:00 - 2:00 PM (ET)
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Application Number: IND 119047
Product Name: ropeginterferon-*a*-2b solution for injection (P1101).
Indication: Treatment of Polycythemia Vera (PV)
Sponsor Name: PharmaEssentia Corporation

Meeting Chair: Tanya Wroblewski, MD
Meeting Recorder: Beatrice Kallungal, MS

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
Tanya Wroblewski, MD, Clinical Team Leader
Patricia Oneal, MD, Clinical Reviewer
Beatrice Kallungal, MS, Senior Regulatory Project Manager

OHOP/Division of Hematology Oncology Toxicology
Simon Williams, PhD, Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Olanrewaju Okusanya, Pharm D, Team Leader
Lauren Price, Pharm D, Reviewer

Office of Biostatistics/Division of Biometrics V
Yeh-Fong Chen, PhD, Team Leader
Yaping Wang, Reviewer

Office of Biotechnology Products (OBP)/Division of Therapeutic Proteins
Harold Dickensheets, PhD, Biologist

Office of Surveillance and Epidemiology (OSE), Office of Medication Error Prevention and Risk Management (OMEPRM), Division of Medication Error Prevention and Analysis (DMEPA)
Hina Mehta, Pharm, Team Leader
Saharat Patanavanich, PharmD, BCACP, Safety Regulatory Project Manager

SPONSOR ATTENDEES

PharmaEssentia Corporation
Albert Qin, MD, PhD, Chief Medical Officer
Craig Zimmerman, PhD, Vice President Medical and Drug Development
Ching-Leou (CL) Teng, PhD, Chief Scientific Officer
Ko-Chung (KC) Lin, PhD, Chief Executive Officer
Chung-Wei Lee, MD, PhD, Director of Clinical Development
Lisa Kang, MS, Executive Director Global Clinical Operations and Biostatistics
Oleh Zagrijtschuk, MD, Director of Medical Affairs and Therapeutic Area Head
Samuel Lin, Sr. Director Business Operations
Marija Sebastian, PhD, Vice President Commercial

Consultants

(b) (4)

1.0 BACKGROUND

The Sponsor, PharmaEssentia Corporation is currently developing Ropeginterferon alpha-2b (PEGylated-proline interferon alpha-2b, P1101) Injection, containing a mono-PEGylated interferon analogue for the treatment of polycythemia vera (PV). This indication was granted Orphan Drug Designation by the Food and Drug Administration (FDA) on April 2, 2012.

Previous interactions with the Agency include:

- (b) (4)
- Type B End of Phase meeting in February 2018 to discuss the proposed design of a new phase III pivotal trial of P1101 in polycythemia vera (PV) patients and to update the Agency on key elements of both the PROUD-PV and CONTINUATION-PV studies used to inform the design of the new phase III study.

- Type B guidance meeting in September 2017 to discuss a relevant high-risk patient population, the relevance of complete hematologic response (CHR) in patients with PV, the relevance of the PROUD-PV study data, and the design of a new supportive study.

- Type B, Pre-Phase 3 meeting in April 2017 to discuss the clinical program, particularly the pivotal Phase III PROUD-PV study (A randomized, open-label, multicenter, controlled, parallel arm phase III study assessing the efficacy and safety of P1101 vs. Hydroxyurea in patients with Polycythemia Vera [PROUD-PV study]), as well as additional clinical studies.

- Type C guidance meeting in April 2019 to discuss an updated P1101 clinical data package and gain agreement on the proposed clinical efficacy endpoint in support of a marketing application for polycythemia vera (PV).

The goal of this pre-BLA meeting is to discuss the proposed format and the adequacy of the available regulatory, clinical, non-clinical and biostatistics issues to support the filing of a proposed BLA for your drug product and its marketing approval in the United States.

FDA sent Preliminary Comments to PharmaEssentia on August 30, 2019.

2. DISCUSSION

Preamble: You have not provided adequate responses to the issues raised regarding the trial design and results as discussed in the meeting from April 11, 2019. We recommend that you provide further clarification and summary results for the Agency to review before we can agree to submission of proposed BLA application. Please address the following issues to include summary data or top-line data results to support your responses:

- Provide detailed description and results as to why 25% of patients discontinued therapy and did not enroll into the CONTINUATION-PV study. As only 75% of the patients, who were randomized to the P1101 arm in the PROUD-PV, were enrolled to the CONTINUATION-PV, this post-hoc patient selection (whether it was caused by study conduct or by patient drop-out) may render the results non-evaluable. Include a discussion of this concern.

- We recommend that the primary endpoint assess complete hematological response (CHR), including phlebotomy ineligibility plus no increase in spleen size. Include topline summary data for this endpoint as well as CHR and CHR with improvement in splenomegaly. In addition, clarify if proposed complete hematological response still includes no phlebotomy eligibility as part of the definition.

- Provide demographic results for number of patients that were treatment naïve and those who had prior HU treatment at time of enrollment into the PROUD-PV study and the number of patients for each of these populations in the CONTINUATION-PV study. Include top-line efficacy results for CHR and CHR with no decrease in spleen size to include prior hydrea use as a stratification factor for both the 12, 24, and 36-month efficacy results. Discuss how any imbalances in these populations may have affected the results.

- In Appendix 8.1, table 1 (percentage allelic burden reduction). The ordinate scale for baseline results is at 40%. Most patients with newly diagnosed PV have allelic burdens around 90%. Please explain this discrepancy.

- Provide a discussion as to the clinical relevance of the greater loss of effect on CHR during the first year of treatment with your drug in comparison to HU.

- Durability of response will be an important consideration. Please include summary of durability of response for CHR and CHR with no increase in spleen size.

- Provide the proposed dosing regimen for P1101 and include any dose modifications due to intrinsic or extrinsic factors. Discuss the data available to support the selection of the recommended dosing regimen in the general PV patient population and specific populations.

- Discuss the impact of the differences in dose titration, pharmacokinetics, and pharmacodynamics of P1101 on the safety and efficacy results in the clinical studies compared to that observed with hydroxyurea.

- [redacted] (b) (4)

- We also note the list of comments provided to you on 8/23/19 regarding CMC issues.

The Agency will need to review these responses before reaching agreement on application submission.

Discussion:
The Agency and Sponsor had a general discussion regarding the proposed BLA submission. The Sponsor provided detailed responses in the slides addressing the issues outlined in the preamble. The Agency also stated that the application will likely be discussed at an advisory committee meeting.

The Sponsor's proposed method for assessment of CHR durability (i.e. number of days starting from assessment visit when the response was achieved till date (excluding) of assessment visit when the response was lost) is reasonable.

The Agency recommended that the Sponsor include the justifications/rationale to the points raised in the preamble in the proposed BLA. In addition, the Agency recommended that you address the following comments in proposed BLA submission:

1. ***Conduct and provide an analysis of depression among patients in both study arms for PROUD-PV and CONTINUATION studies.***
2. ***Differences in the rate of CHR and rate of CHR with no increase of spleen size among those 21 patients who discontinued during the PROUD study and the 11 patients who completed PROUD study and did not enroll in the CONTINUATION-PV study.***
3. (b) (4)
4. ***Analysis of allelic burden and treatment-emergent adverse events (i.e thromboembolic events).***
5. ***Presence of other mutations (i.e. TET2) impacting the response to therapy in the presence of JAK2 mutation or mutation profile over time, if available.***

The Agency recommended that the Sponsor submit their Human Factor study protocol separately to the existing IND.

Post-meeting comments: We acknowledge the submission of the Human Factor (HF) study protocol on September 11, 2019. The Agency will review the HF protocol and provide written comments within 60 days of the submission. In order to perform an efficient BLA review, we require that the results of the HF validation study are submitted no more than 30 days after the BLA is submitted.

We ask the Sponsor take this into consideration in regards to the development timeline of the proposed product.

Question 1: *Would the Agency please clarify Item 4 in the April 11, 2019 FDA meeting minutes Post Meeting Addendum: Discussion of the allelic frequency and responses at different timepoints (12, 24, 36 months) between treatment arms? By responses, does the Agency mean the change in allelic frequency and molecular response, as well as complete hematological response (CHR)?*

FDA Response to Question 1: The Agency recommends that you include an assessment of the change from baseline in the allelic frequency, molecular response and complete hematological response at specified timepoints (for example 12, 24 and 36 months). In addition, include durability of the responses. Please also see the Preamble regarding the baseline allelic frequency.

Discussion:
No discussion.

Question 2: *Would the Agency please clarify Item 6 in the April 11, 2019 FDA meeting minutes Post Meeting Addendum: Justification that post-hoc selection of endpoints allows for internal and external validation of study results. Which endpoints does the Agency refer to, and what is meant by internal and external validation in this context?*

FDA Response to Question 2: You will need to provide evidence that the change in the non-inferiority (NI) margin from (b) (4) (post-hoc) did not affect the final outcome of primary endpoint of complete hematological response. In addition, we recommend that you evaluate CHR and no increase of spleen size and submit summary data for both CHR and no increase in spleen size and CHR.

Internal validity is a measure of the accuracy of the trial and the extent to which the study results are free from errors and any difference in measurement is due to independent variable and not attributed to anything else. External validity is the extent to which the results can be generalized to the proposed population. You will need to discuss how the change in the NI margin post-hoc does not affect internal validity (that there are no other variables affecting results) and if results can be generalized to the population.

Discussion:
No discussion.

Question 3: *PharmaEssentia has conducted an extensive ICH S6 (R1)-compliant nonclinical development program for ropeginterferon alfa-2b. Based on the information summarized in Section 6.1, does the Agency agree that the completed nonclinical studies provide the necessary information to support the submission and approval of the BLA?*

FDA Response to Question 3: Yes, we agree that your nonclinical studies package is adequate, however please see Preamble.

Discussion:
No discussion.

Question 4*: Since the nonclinical studies were completed in 2008 and 2009, prior to the introduction of SEND, PharmaEssentia does not plan to submit CDISC-compliant SEND nonclinical datasets. Does the Agency agree the approach is adequate to support the filing of the BLA for ropeginterferon alfa-2b?*

FDA Response to Question 4: We agree that the nonclinical datasets do not need to be SEND-compliant, however please see Preamble.

Discussion:
No discussion.

Question 5*: PharmaEssentia thus believes that there is enough information from prior clinical studies with related products and does not plan to conduct a dedicated renal impairment study with ropeginterferon alfa-2b. Does the Agency agree with the Sponsor's approach?*

FDA Response to Question 5: No. You should characterize the effect of severe renal impairment on the pharmacokinetics of ropeginterferon alfa-2b to support dosing recommendations or provide adequate justification for why pharmacokinetic characterization was not completed in these patients in the BLA submission. Data from other drug products cannot be used to support dosing recommendations for ropeginterferon alfa-2b in patients with severe renal impairment.

Ropeginterferon alfa-2b will be regulated under a Biologics License Application (BLA). There is no regulatory BLA pathway equivalent to a 505(b)(2) NDA, which allows reliance on the Agency's previous findings of safety and efficacy as reflected in approved labeling. Therefore, you may not rely on the package insert of other drug products to support submission of your BLA. You also may not rely on published literature reporting the results of studies conducted with interferon products approved or under development for which you do not have a written right of reference.

Discussion:
No discussion.

Question 6*: PharmaEssentia is not planning to conduct additional drug-drug interaction studies. Does the Agency agree with the Sponsor's approach?*

FDA Response to Question 6: See response to Question 5 regarding reliance on other drug products or published literature. You will need to provide data describing the effect of ropeginterferon alfa-2b on the activity of cytochrome P450s or provide a detailed justification for why drug interaction studies are not conducted and included in the BLA submission. The adequacy of the provided drug interaction information will be a review issue.

Discussion:
No discussion.

Question 7: *PharmaEssentia is* (b) (4) *Does the Agency agree the Sponsor's plan is adequate to support filing of the BLA?*

FDA Response to Question 7: (b) (4)

Discussion:
No discussion.

Question 8: *PharmaEssentia is not planning to conduct a formal investigation on the metabolism and excretory pathway of ropeginterferon alfa-2b. Does the Agency agree the Sponsor's plan is adequate to support filing of the BLA?*

FDA Response to Question 8: See response to Question 5 regarding reliance on other drug products or published literature. You will need to provide data describing the metabolism and elimination of ropeginterferon alfa-2b or provide a detailed justification for why metabolism and elimination studies were not conducted and included in the BLA submission. The adequacy of the provided metabolism and elimination information will be a review issue.

Discussion:
No discussion.

Question 9: *The Summary of Clinical Pharmacology Studies (Module 2.7.2) will include the rationale for the proposed dose regimen for ropeginterferon alfa-2b, including comparisons of PK with hydroxyurea and other marketed pegylated interferons to support filing of a BLA for ropeginterferon alfa-2b (Section 6.2.8). Does the Agency agree the Sponsor's plan is adequate to support filing of the BLA?*

FDA Response to Question 9: The adequacy of the dose rationale will be a review issue. See Additional Clinical Pharmacology Comments for advice in preparing the clinical pharmacology sections of the BLA. In addition, please see Preamble.

Discussion:
No discussion.

Question 10*: Does the Agency agree that the SAS programs used to generate the CSR tables, figures, and listings for PEGINVERA, PROUD-PV, and CONTINUATION-PV studies should be submitted to support the filing of the BLA for ropeginterferon alfa-2b?*

FDA Response to Question 10: You have not provided sufficient responses to issues raised in the prior meeting from April 11, 2019, therefore we do not agree with proposed submission at this time.

In general, all programs should be thoroughly commented:

- Please include an index of the programs that were used to produce tables and figures in the main text portion of the CSR.
- Please ensure that the dataset file names are consistent with those or being called in the programs, so that the Agency can use them to verify your results/figures/tables.

- Please include annotations for tables and figures in the main text portion of the CSR. The annotations should indicate which analysis dataset variables were used to produce the tables or figures.

Please also see Preamble.

Discussion:
No discussion.

Question 11: *For studies not included in the ISS, the clinical study adverse events are coded with MedDRA version 18.1 and medications are coded with WHODrug September 2015. Does the Agency agree that these are acceptable?*

FDA Response to Question 11: See Preamble. The proposed coding with MedDRA version 18.1 and medications coded with WHODRUG September 2015 are reasonable as the study was initiated after March 15, 2019. Please note that for studies starting after March 15, 2019, submissions will be required to use the B3-format of WHODrug Global.

Discussion:
No discussion.

Question 12: *PharmaEssentia plans to include the Phase 3 PROUD-PV, Phase 3b CONTINUATION-PV,* [redacted] (b) (4) *and Phase 1/2 PEGINVERA data in the ISS. More, PharmaEssentia plans to discuss the ISS analyses in Module 2 of the CTD without providing separate ISS reports in Module 5. Does the Agency agree that this approach is acceptable?*

FDA Response to Question 12: We do not agree with submission of BLA at this time. See preamble. For future reference, it is acceptable to split the ISS between Module 2 (section 2.7.4) and Module 5 with the ISS containing text (with incorporated tables and figures) and the appendices and datasets placed in Module 5 (section 5.3.5.3). Section 2.7.4 should refer the reader to section 5.3.5.3 for the appendices and datasets and section 5.3.5.3 should refer the reader to section 2.7.4 for the text portion of the ISS.

Discussion:
No discussion.

Question 13*: Since all data from the original European patient case report forms (CRFs) were incorporated into the raw data sets, PharmaEssentia does not plan to submit individual patient CRFs for deaths, serious adverse events, or withdrawals due to adverse events with the BLA. Does the Agency agree that this is acceptable?*

FDA Response to Question 13: No, per US 21 CFR 314.50 individual subjects CRFs should be submitted for subjects who died or who did not complete the study due to an adverse event and SAEs.

Discussion:
No discussion.

Question 14*: Does FDA agree that an ISE will not be required for this BLA submission? Does the Agency agree that this is acceptable?*

FDA Response to Question 14: We do not agree with submission of BLA at this time. For future reference it is acceptable to for the Summary of Clinical Efficacy (SCE) to serve as the ISE if appropriate data can be included within the space limitations of the SCE. You will need to include a reference page in Module 5.3.5.3 stating the SCE in Module 2, section 2.7.3 serves as the ISE. We refer you to the following guidance: Integrated Summary of Efficacy: Guidance for Industry
at https://www.fda.gov/media/72335/download.

Discussion:
No discussion.

Question 15*: Does FDA agree that this approach to providing evidence of efficacy in the BLA is appropriate?*

FDA Response to Question 15: No, we don't agree with submission of the BLA at this time. Please see Preamble. We also recommend that you evaluate CHR with no increase in splenomegaly.

We reiterate that we have concerns with the results of the original study and analysis plan are problematic to support an approval. Even with detailed responses, the data and results in aggregate still pose significant challenges in defining appropriate population and clinical benefit.

Discussion:
No discussion.

Question 16: *Does FDA agree with the following analyses for key secondary endpoints and other secondary endpoints that will provide supportive information to the efficacy of P1101?*

Key secondary endpoints

1. *Change in hematologic parameters, Hct, WBCs, PLTs and red blood cells (RBCs), from baseline (i.e., "EoT visit" in the PROUD-PV study) over time up to last patient visit.*
2. *Change in JAK2 allelic burden from baseline ("EoT visit" of the PROUD-PV study) over time up to last patient's last visit.*

Other secondary endpoints

1. *Change of disease-related signs and disease-related symptoms (microvascular disturbances, pruritus, headache).*
2. *Change in QoL (EQ-5D-3L) from baseline ("EoT visit" of the PROUD-PV study) over time up to last patient visit.*

FDA Response to Question 16: No. We do not agree with the "other secondary endpoints". Given the limitations and failures of the original study design and results of the PROUD-PV study and open-label nature of the PV-CONTINUATION study no definite conclusions can be made regarding these "other secondary endpoints". In addition, the change of disease-related signs and symptoms and QOL may be biased and open to intra-patient and intra-investigator subjectivity.

Please also see the Preamble.

Discussion:
No discussion.

Additional Clinical Pharmacology Comments:

Recommendation about labeling:

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.

Address the following questions in the Summary of Clinical Pharmacology:

1. What is the basis for selecting the doses and dosing regimen used in the registration trials 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 (such as 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. Provide a summary of the available Clinical Pharmacology information using the attached Table 1.

2. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.

3. 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.

4. 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.

5. 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.

6. 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)

7. 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.

Table 1: Highlights of Clinical Pharmacology

General Information	
Chemical structure and major physical and chemical properties	• Include log P, pKa, solubility (in water and buffers at different pH levels) if oral drug product • Include chemical structure and molecular weight

Indication		• Include the proposed indication • Include other relevant indications under different INDs
Route of administration and formulation type and strengths		• Specify if oral, IV, SC or topical administration • Specify tablet, capsule, intravenous solution or lyophilized powder • List which formulation used in each clinical trial and provide a comparability or bioavailability data for the different products
Mechanism of action		• List proposed mechanism of action for this indication • List proposed mechanism of action for other indications if relevant
Dose and Adverse Events		
Therapeutic dose and exposure		• List proposed clinical dosing regimen for this indication • List proposed clinical dosing regimen for other indications • Provide mean (%CV) C_{max} and AUC at the maximum administered single dose • Provide mean (%CV) C_{max} and AUC at steady state following the administration of the proposed clinical dose
Maximum tolerated dose		• List MTD or OBD identified in clinical trials • Provide the HNSTD or NOAEL
Major adverse events		• List most common adverse events • List dose limiting adverse events • Describe dose or exposure related adverse events • Provide the median time to first and subsequent dose modifications and the reason for these modifications
Pharmacokinetic (PK) Features		
Dose or exposure range tested in clinical trials	Single Dose	• Dose range • Mean (%CV) Cmax and AUC range
	Multiple Dose	• Dose range, dosing interval and duration • Mean (%CV) C_{max} and AUC
Range of linear PK		• Linear dose range • Non-linear dose range
Accumulation at steady state		• Dose range, dosing interval and duration • Mean (%CV) for parent and clinically relevant metabolites
Metabolites		• List relevant (active or major) metabolites • Describe safety and activity (e.g., receptor binding)
Absorption	Bioavailability	• Mean (%CV)
	T_{max}	• Median (minimum, maximum) for parent • Median (minimum, maximum) for metabolites
Distribution	Vd/F or Vd	• Mean (%CV)
	Protein binding (%)	

	Blood to plasma ratio	
Elimination	Route	• Summarize findings of mass balance study in nonclinical and clinical studies • Specify primary route and percentage dose eliminated (parent, metabolites). • List other routes
	Half-life	• Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	• Mean (%CV)
Metabolism	• by CYP ☐ Yes ☐ No ☐ NA, if yes, specify • by Phase II enzymes ☐ Yes ☐ No ☐ NA • by other enzyme systems ☐ Yes ☐ No ☐ NA, if yes, specify • Inhibits CYP ☐ Yes ☐ No ☐ NA, if yes, specify and provide Ki or IC50. • Inhibits Phase II enzymes ☐ Yes ☐ No ☐ NA, if yes specify and provide Ki or IC50. • induces CYP ☐ Yes ☐ No ☐ NA, if yes specify	
Transporters	• by major transporters ☐ Yes ☐ No ☐ NA, if yes, specify • Inhibits major transporters ☐ Yes ☐ No ☐ NA, if yes, specify and provide Ki or IC50. • induces major transporters ☐ Yes ☐ No ☐ NA, if yes specify	
Intrinsic Factors	Age	Geriatric patients: • Age range • Mean changes in C_{max} and AUC
		Pediatric patients: • Age range/pediatric subpopulations • Mean difference in C_{max} and AUC
	Sex	• Mean difference in C_{max} and AUC
	Race	• Mean difference in C_{max} and AUC
	Hepatic impairment	• Mean difference in C_{max} and AUC
	Renal Impairment	• Mean difference in C_{max} and AUC
	Weight	• Mean changes in C_{max} and AUC
Extrinsic Factors	Drug interactions (including gastric acid reducing agents)	• List DDI studies with geometric mean ratio for C_{max} and AUC of parent, metabolites or total analyte
	Food effects	• Geometric mean ratio for C_{max} and AUC • Specify meal type (i.e., high-fat, standard, low-fat)
Population PK Analyses		• Provide data source listing • Summarize results
Pharmacodynamic (PD) Features		
PD Studies:		

e.g.: QT effect, receptor occupancy, biomarkers	
Analyses for E-R relationships	
Other Studies	
e.g., Genotyping	

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The Sponsor stated that they intend to submit a complete application and therefore, there are no agreements for late submission of application components.

- 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 and it was concluded that at this time, the Agency does not see the need for REMS, however the Agency reserves a final decision on the need for a REMS until after the review team has fully reviewed the data that is to be submitted.

- 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: Human Factor (HF) validation study.

  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:

  NDA/BLA NUMBER: LATE COMPONENT - CLINICAL

In addition, we note that a chemistry pre-submission meeting was held on August 28, 2019. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

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 any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined 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. See link to list of relevant molecular targets below. 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 include plans 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*.

For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult FDA's Guidance on Formal Meetings Between the FDA and Sponsors or Applicants[3] to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[4]

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[5] and Pregnancy and Lactation Labeling Final Rule[6] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[3] See the guidance for industry *"Formal Meetings Between the FDA and Sponsors or Applicants."*
[4] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[5] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[6] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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*.

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The

meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

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 FDA.gov.[7]

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

[7] http://www.fda.gov/ectd

specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[8]

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

[8] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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*.[9]

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[10]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- AssessmentAid[11]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming*

[9] https://www.fda.gov/media/85061/download
[10] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[11] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

of Biological Products, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

Your proposed 351(a) BLA would be within the scope of this guidance. As such, FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items for this meeting.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor's response to the meeting preliminary comments was used during the meeting discussions and has been appended to these meeting minutes.

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/s/

TANYA M WROBLEWSKI
09/19/2019 12:07:27 PM

IND 119047

MEETING MINUTES

PharmaEssentia Corporation
C/o PharmaEssentia US, LLC
Attention: Craig Zimmerman, PhD
Vice President Medical and Drug Development
35 Corporate Drive, Suite 325
Burlington, MA 01803

Dear Dr. Zimmerman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ropeginterferon-*a*-2b solution for injection (P1101).

We also refer to the meeting between representatives of your firm and the FDA on August 29, 2019. The purpose of the meeting was to to discuss the content and format as well as the general technical information of Module 3 (quality) to be submitted with the Biologics License Application, (BLA).

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

If you have any questions, call Florence Aisida, Regulatory Business Process Manager, at (240) 402-2691.

Sincerely,

{See appended electronic signature page}
Raymond P. Donnelly, Ph.D.
Team Leader – Product Quality
Division of Biotechnology Review and Research II
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
- Meeting Summary

U.S. FOOD & DRUG ADMINISTRATION

MEETING SUMMARY

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: August 28,2019, 1:00 p.m.- 2:00 p.m.
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room:1311
Silver Spring, Maryland 20903

Application Number: IND 119047
Product Name: ropeginterferon-*a*-2b solution for injection (P1101)
Indication: Treatment of adults with polycythemia vera without symptomatic splenomegaly
Sponsor Name: PharmaEssentia Corporation

Meeting Chair: Raymond P. Donnelly, Ph.D.
Meeting Recorder: Florence Aisida, Pharm D ,B.C.P.S

FDA ATTENDEES

Jessica Hankins Ph.D. Microbiology reviewer, OPF/ OPQ/CDER/FDA
Harold Dickensheets, Ph.D., OBP/OPQ/CDER/FDA
Maria Cecilia Tami, Ph.D., Review Chief (Acting) OBP/OPQ/CDER/FDA
Guo Rong, CDRH/ FDA
Raymond Donnelly, Ph.D., Team Lead OBP/OPQ/CDER/FDA
Patricia Hughes, Ph.D., Branch Chief, OPF/ OPQ/CDER/FDA

SPONSOR ATTENDEES

Albert Qin MD, PhD, Chief Medical Officer
Craig Zimmerman, PhD, Vice President, Medical and Drug Development
Ching-Leou (CL) Teng, PhD, Chief Scientific Officer
Ko-Chung (KC) Lin,PhD ,Chief Executive Officer
Chung-Wei Lee MD, PhD,Director of Clinical Development
Samuel Lin ,Sr. Director Business Operations
Marija Sebastian, PhD, Vice President Commercial
Chao-Sheng (James),Cheng, PhD Senior Director of Biologics Manufacturing
Duu-Gong Wuu ,PhD Regulatory Consultant to PharmaEssentia
Patricia Mann ,Regulatory Consultant to PharmaEssentia
Yengung Luan,MS,General Manager & Head of Bioprocess Development

1.0 BACKGROUND

Ropeginterferon alfa-2b Injection, containing a mono-PEGylated interferon analogue, has been developed by PharmaEssentia Corporation for the treatment of polycythemia vera (PV). Orphan Drug Designation was granted to ropeginterferon alfa-2b for the treatment of PV by the European Medicines Agency (EMA) on December 09, 2011 and by the FDA on April 2, 2012 (Orphan Drug Designation number #12-3670).

The purpose of this meeting was to acquaint the Agency with the content and format as well as the general technical information of the chemistry, manufacturing, and controls (CMC) information to be submitted with the BLA to discuss the best approach for the presentation of key data and formatting of Module 3 (quality) in the final application.

Before the meeting, the Sponsor provided additional information to address some of the comments from FDA. This information is attached to these meeting minutes. The Sponsor also provided a presentation with the responses they wanted to discuss during the meeting. The presentation is also attached to these meeting minutes.

2. DISCUSSION

Question 1: Does the Agency agree that the CMC information as outlined in the attached quality summary document for drug substance and drug product is adequate to support the filing of a BLA?

FDA Response to Question 1: No, the Agency does not agree. We have the following requests for information.

Product Quality:

(b) (4)

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(b) (4)

[redacted]

Device content for marketing application
Device information should be located in the appropriate eCTD module, as recommended in the FDA's eCTD Technical Conformance Guide: Technical Specifications Document: "Guidance for Industry Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" (https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf).

When submitting a marketing application for the final finished combination product, provide the following information related to your device:

1) Device Description Documentation

a) Provide a description of your device constituent design, including any novel features and/or functionalities. This should include drawings / diagrams of the device, descriptions of device components, or any other available information to explain the device design.

b) Describe the principles of operation of your device.

c) Describe any accessories or other devices labeled for use with your device (e.g., co-packaged needle).

2) Design Control (21 CFR 820.30) – The application should include design documentation. The use of recognized standards and FDA guidance to inform design and testing is recommended, as applicable. For questions about design control documentation, we recommend that you reference the FDA Design Control Guidance for Medical Device Manufacturers, https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm070642.pdf. We recommend that the design control information provided in your application include the following:

a) Design Input Requirements (e.g., safety, performance, and reliability requirements of a device that are used as a basis for device design)

b) Design Output Specifications (e.g., device description, drawings, specifications, bill of materials, etc.)

c) Design Verification Plan/Summary Report, supporting data and traceability

d) Design Validation Plan/Summary Report, supporting data and traceability

e) Risk Management File

3) Essential Performance – Identify essential performance requirements (EPR) for the device.

For each identified essential performance requirement, your marketing application should include verification and validation information of EPR specifications. While the final set of essential performance requirements should be based on your design control process, we are providing the following example EPRs for your device type. This is not an exhaustive list and product specific factors should influence your EPR selection.

Example prefilled syringe EPRs:

- Delivered Volume Accuracy
- Break loose & Extrusion Force

4) Additional testing – Regarding your device constitute type, provide luer connection testing compliance to ISO 80369.

5) Stability (ICH Q1) – Your stability program should include endpoints to verify that device essential performance is maintained at expiry. You may exclude certain EPRs from the stability study if you can provide scientific rationale that the excluded EPR is unlikely to change over time.

6) Shipping - Provide documentation for the final finished product to demonstrate that the device EPRs are met after shipping.

7) Control Strategy – Provide a control strategy that ensures that the final finished combination product maintains its essential performance requirements. The control strategy may consist of, but is not limited to, lot release, in-process, control of incoming materials, purchasing controls, etc.

8) Quality System – The marketing application should contain a complete summary of your base operating system as described in the FDA guidance titled Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products issued in January 2017 **(https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf).**

Meeting Discussion:

The Sponsor asked these questions during the meeting:

- **The Human Factor/Usability Study Protocol was provided for Agency's review as Appendix C in the preBLA CMC meeting briefing package** (b) (4) [redacted]
- [redacted] (b) (4)

- [redacted] (b) (4)

The agency responded by stating that the clinical review team needs to provide responses to these two questions and suggested a separate meeting or WRO request be submitted to address these specific questions. The Agency also agreed to forward their questions to the clinical division for a response.

PharmaEssentia is planning to submit their BLA by December.

The FDA asked the Sponsor to provide clarification [redacted] (b) (4)

The FDA reiterated that the BLA submission should include data to support physicochemical stability of the DS and DP after shipping. The sponsor explained that they have not yet identified a distributor for the DP and, therefore, they have not yet conducted the necessary shipping validation studies. They proposed to provide a shipping validation protocol in the BLA submission. The Agency explained that the Sponsor should provide in the BLA results from simulated shipping studies perfomed under worst case conditions, in addition to a protocol for real time shipping validation studies.

3.0 ATTACHMENTS AND HANDOUTS

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/s/

BAMIDELE F AISIDA
09/20/2019 10:40:46 AM

RAYMOND P DONNELLY
09/20/2019 11:17:38 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 119047

MEETING MINUTES

PharmaEssentia Corporation
(b) (4)

Dear (b) (4):

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Pegylated-proline interferon α-2b solution for injection (P1101).

We also refer to the meeting between representatives of your firm and the FDA on February 15, 2018. The purpose of the meeting was to discuss the proposed design of a new phase III pivotal trial of P1101 in PV patients and to update the Agency on key elements of both the PROUD-PV and CONTINUATION-PV studies used to inform the design of the new phase III study.

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}

Nicole Gormley, MD
Clinical Team Lead
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
Meeting Date and Time:	February 15, 2018; 3:00-4:00PM (ET)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1311 Silver Spring, Maryland 20903
Application Number:	IND 119047
Product Name:	Pegylated-proline interferon α-2b solution for injection (P1101)
Indication:	Treatment of Polycythemia Vera (PV)
Sponsor/Applicant Name:	PharmaEssentia Corporation
Meeting Chair:	Nicole Gormley, MD
Meeting Recorder:	Rachel McMullen, MPH, MHA

FDA ATTENDEES

Office of Hematology and Oncology Products/Division of Hematology Products (DHP)

Albert Deisseroth, MD, PhD, Supervisory Associate Deputy Director
Nicole Gormley, MD, Clinical Team Leader
Andrea Baines, MD, PhD, Medical Officer
Rachel McMullen, MPH, MHA, Senior Regulatory Project Manager

Office of Biostatistics/Division of Biometrics V

Thomas Gwise, PhD, Deputy Director
Xin Gao, PhD, Statistical Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V

Olanrewaju Okusanya, PhD, Acting Clinical Pharmacology Team Leader

SPONSOR ATTENDEES

PharmaEssentia Corporation

Oleh Zagrijtschuk, MD, Therapeutic Area Head
Albert Qin, MD, PhD, Chief Medical Officer
Craig Zimmerman, PhD, Vice President of US Operations
Ching-Leou Teng, PhD, Chief Scientific Officer
Ko-Chung Lin, PhD, Chief Executive Officer

Samuel Lin, Director of Operations
Chung-Wei Lee, MD, Director of Clinical Development

Consultants:

(b) (4)

Via Telephone:

(b) (4)

1.0 BACKGROUND

The Sponsor, PharmaEssentia Corporation, is currently developing Ropeginterferon alpha-2b (PEGylated-proline interferon alpha-2b, P1101) Injection, containing a mono-PEGylated interferon analogue for the treatment of polycythemia vera (PV). This indication was granted Orphan Drug Designation by the Food and Drug Administration (FDA) on April 2, 2012.

The Sponsor had a Type B, Pre-Phase 3 meeting with the Agency in April 2017 to discuss their clinical program, particularly the pivotal Phase III PROUD-PV study (A randomized, open-label, multicenter, controlled, parallel arm phase III study assessing the efficacy and safety of P1101 vs. Hydroxyurea in patients with Polycythemia Vera [PROUD-PV study]), as well as additional clinical studies.

The Sponsor also had a Type B meeting with FDA on September 20, 2017 to discuss a relevant high-risk patient population, the relevance of complete hematologic response (CHR) in patients with PV, the relevance of the PROUD-PV study data, and the design of a new supportive study.

In December 2017, the Sponsor requested a Type B meeting to discuss the proposed design of a new phase III pivotal trial of P1101 in PV patients and to update the Agency on key elements of both the PROUD-PV and CONTINUATION-PV studies used to inform the design of the new phase III study.

FDA sent Preliminary Comments to PharmaEssentia on February 6, 2018

2. DISCUSSION

Question 1: *Does FDA agree that the proposed study inclusion / exclusion criteria are appropriate for conducting a pivotal phase III clinical study of P1101 in PV?*

FDA Response: Your proposed eligibility criteria appear reasonable.

However, we reiterate our prior comment (conveyed 9/14/17) that the inclusion criterion for renal function be CrCL ≥ 60 mL/min using the Cockcroft-Gault equation, or estimated GFR ≥ 60 mL/min/1.73 m^2 using the MDRD equation.

DISCUSSION: There was no discussion.

Question 2: *Does FDA agree that the proposed study design is acceptable for a pivotal phase III study of P1101 in PV?*

FDA Response: In general, your proposal for a randomized, controlled study comparing P1101 to best available therapy (BAT) appears reasonable, however, we have the following concerns:

a. You propose to include multiple agents as BAT. However, there is significant heterogeneity among these agents, with differing mechanisms of action and toxicity profiles, which may make comparisons between P1101 and BAT more challenging.
b. Several of the proposed options for BAT are not approved or marketed in the U.S. You should justify the options for BAT and ensure that they are representative of standard of care practices in the U.S.
c. Among the BAT options, you propose to include phlebotomy and aspirin. Provide a justification for inclusion of phlebotomy and aspirin in light of your proposed patient population (e.g. patients with severe thrombosis).
d. The design allows patients to cross over from the control arm to the treatment arm before the primary endpoint is completely assessed. We are concerned that this may bias the analysis results.
e. Your proposed definition of treatment failure is based on treatment-related toxicity; however, the definition of treatment failure should be based on disease progression or disease-related symptoms.
f. We discourage any crossover during the dose titration period. Please clearly define progression of disease and treatment failure as the criteria for crossover and consider patients from both treatment groups who meet the criteria of treatment failure or progression of disease as non-responders.
g. Please provide the detailed definition of the secondary endpoints including PRO endpoints.
h. Please specify the analyses methods for efficacy endpoints including PRO endpoints.
i. Please add a multiplicity adjustment procedure to control the study wise type I error rate at 2-sided 0.05.
j. Please add the missing data analyses methods in the protocol.
k. In the meeting package, you proposed to use intent to treat (ITT) population as the primary analyses population. Please document this plan in the study protocol as well.
l. Please specify how each secondary efficacy endpoint will be handled for cross over patients.
m. The expected study dropout rate and planned number of patients enrolled is inconsistent between section 9 of the meeting package and in the protocol. Please clarify the anticipated dropout rate and planned number of patients enrolled.
n. Please submit the SAP to the agency for review. The Agency may have further comments upon receiving it.

We do not agree with the proposed dosing scheme as it may be sub-optimal. We reiterate our twice conveyed (4/21/17 and 9/14/17) prior recommendations that you perform population PK analysis, E-R analyses of PD markers, and efficacy and safety measurements, to justify the proposed starting dose and dose titration. The analyses should address the questions including (but not limited to):

a) What is the most appropriate starting dose?
b) What is the most appropriate titration schedule?
c) Should a patient-specific starting dose or dose titration be selected based on patients' baseline information?

We reiterate our prior recommendation (conveyed 9/14/17) that you characterize the development of anti-product antibodies to both PEG chains and interferon.

We recommend that you collect pharmacokinetic samples in all patients (i.e., should not be optional) enrolled in trials intended to demonstrate safety and efficacy to perform population pharmacokinetic and exploratory exposure-response analyses. Such trials generally have richer clinical outcome data than other trials and therefore, generally provide a greater opportunity for correlating drug exposure with clinical outcomes.

DISCUSSION: The Sponsor stated that the proposed BAT options were selected to reflect treatment practices in all countries of the proposed global trial. The Agency cautioned that if a substantial proportion of patients on the control arm receive BAT options that do not reflect standard clinical practice in the U.S., there is a risk of not having enough information on which to base a regulatory decision for the U.S. population. The Agency stated that the Sponsor could consider placing a limit on the percentage of patients on the BAT arm receiving non-hydroxyurea therapies.

The Sponsor stated that the option for aspirin and phlebotomy on the BAT arm is only intended for your patients with progressive symptomatic disease or splenomegaly. Because aspirin and phlebotomy alone would not be appropriate for high risk patients, the Agency stated that the protocol should clearly specify which patients are appropriate for this BAT option.

The Agency reiterated its concern that the Sponsor's plan to allow crossover from the BAT arm to the P1101 arm before analysis of the primary endpoint at 24 months may introduce bias. The Agency explained that because this is an open-label trial, there is concern that patients may crossover for reasons that are not objective. Because there is a chance that patients who crossover may have eventually achieved a response if they had stayed on the BAT arm, but would no longer be available for analysis of response on the BAT arm, this may artificially lower the response rate on the BAT arm relative to the P1101 arm. The Sponsor stated that they would provide clarification of the terms and definitions regarding crossover and treatment failure, along with details of the planned statistical analysis in a future revised protocol and Statistical Analysis Plan.

Question 3: *Does FDA agree that the proposed primary efficacy endpoint is appropriate for a pivotal phase III clinical study of P1101 in PV?*

FDA Response: We have concerns with the proposed time points for the analysis of the composite endpoint. You have not provided adequate justification for the time points you have selected. In general, landmark analyses may not provide sufficient evidence of efficacy to support labeling or regulatory decisions. Specifically, you will need to provide data to support the clinical relevance of the 21- and 24-month time points for assessment. Alternatively, you may wish to consider a primary endpoint based on a time-to-event analysis, such as time to disease progression.

We agree with inclusion of resolution of splenomegaly as a component of the composite endpoint; however, we recommend that you use more objective means to assess splenomegaly (e.g., imaging).

DISCUSSION: The Sponsor stated that the planned time points for analysis of the primary endpoint was based on the results of their PROUD-PV and CONTINUATION-PV studies, which showed superiority of P1101 versus BAT measured as a durable hematologic response at 21-24 months. The Agency reiterated concerns with the proposed time points and clarified that the Sponsor should provide external data and published literature to support the clinical relevance of a durable response at 21-24 months.

The Sponsor stated that it would be extremely difficult to design a study with a primary endpoint based on a time-to-event (TTE) analysis, such as time to disease progression, due to the small number of events. The Agency stated that the Sponsor could consider a TTE endpoint that would capture a broader range of clinically relevant events. If a TTE analysis would not be feasible due to a small number of events, it would be helpful for the Sponsor to provide data from the literature to support the lack of feasibility.

The Agency also expressed concern for the potential impact of dropouts, given the planned analysis of the primary endpoint at 21-24 months.

In addition, the Agency sought clarification on the Sponsor's plan for inclusion of patients with splenomegaly and assessment of non-palpable spleen at 24 months as part of the composite primary endpoint. The Sponsor agreed to provide further written clarification as a post-meeting follow-up.

3.0 OTHER IMPORTANT MEETING INFORMATION

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. 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.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the

Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog)
(See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data*
(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide)
(See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* 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.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards 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. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found
at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.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 the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. 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.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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.

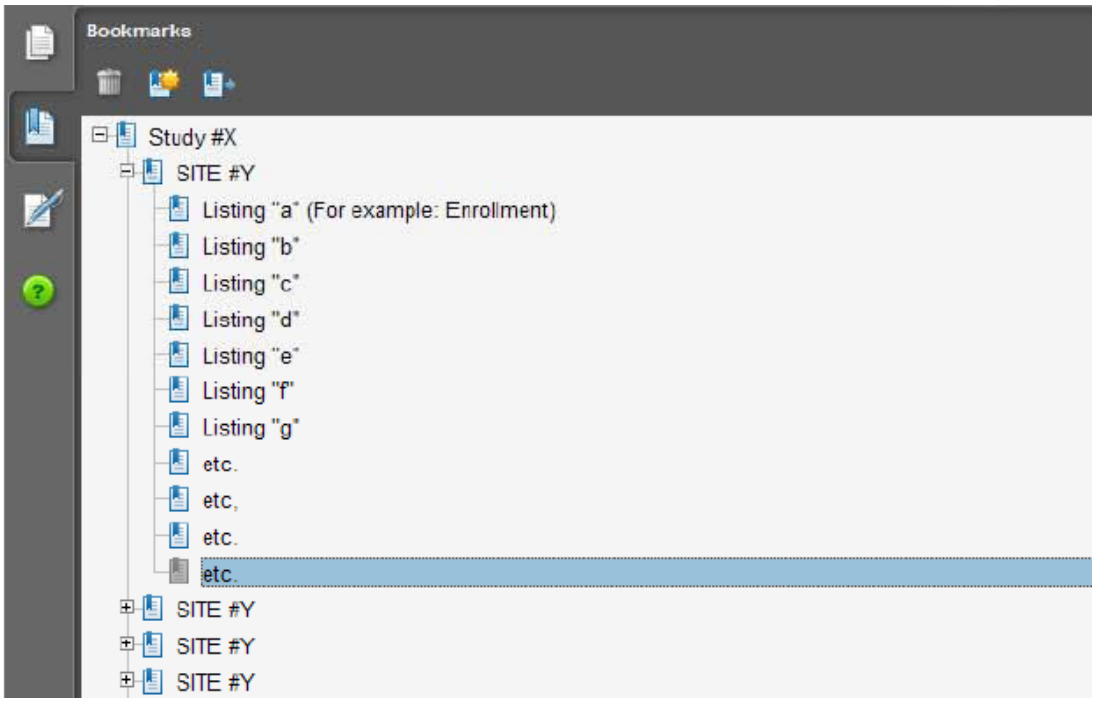
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

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

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

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 is attached for reference.

13 Pages 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/

NICOLE J GORMLEY
02/16/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 119047

MEETING MINUTES

PharmaEssentia Corporation
(b) (4)

Dear (b) (4)

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Repeginterferon Alfa-2b.

We also refer to the meeting between representatives of your firm and the FDA on April 20, 2017. The purpose of the meeting was to discuss the clinical program, particularly the pivotal Phase 3 PROUD-PV study (a randomized, open-label, multicenter, controlled, parallel arm, phase 3 study assessing the efficacy and safety of P1101 vs. hydroxyurea in patients with polycythemia vera), as well as obtain guidance/concurrence on the adequacy of the clinical data to support a future BLA filing.

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}

Nicole J. Gormley, MD
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-Phase 3
Meeting Date and Time:	Thursday, April 20, 2017, 1:00PM-2:00PM ET
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room 1313 Silver Spring, MD 20903
Application Number:	IND 119047
Product Name:	Pegylated Proline Interferon Alpha-2b (P11010 and Repeginterferon Alfa-2b (AOP2014)
Indication:	Treatment of polycythemia vera
Sponsor/Applicant Name:	PharmaEssentia Corporation
Meeting Chair:	Nicole J. Gormley, MD; 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
Edvardas Kaminskas, MD, Deputy Division Director
Nicole Gormley, MD, Clinical Team Leader
Andrea Baines, MD, PhD, Medical Officer
Rachel McMullen, MPH, MHA, Senior Regulatory Project Manager

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Stacy Shord, Pharm D, Clinical Pharmacology Team Leader
Liang Li, PhD, Clinical Pharmacology Reviewer

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

Office of Pharmaceutical Quality
Harold Dickensheets, PhD, Product Quality Reviewer

SPONSOR ATTENDEES

PharmaEssentia Corporation
Oleh Zagrijtschuk, MD, Therapeutic Area Head

Albert Qin, MD, PhD, Chief Medical Officer
Craig Zimmerman, PhD, Vice President of US Operations
Ching-Leou Teng, PhD, Chief Scientific Officer
Kochung Lin, PhD, Chief Executive Officer
Shufen Li, PharmaEssentia

Consultants

(b) (4)

1.0 BACKGROUND

Based on previous discussion in (b) (4). submitted a Type B meeting on behalf of PharmaEssentia Corporation on February 17, 2017, to discuss the clinical program, particularly the pivotal Phase III PROUD-PV study (A randomized, open-label, multicenter, controlled, parallel arm phase III study assessing the efficacy and safety of P110 vs. Hydroxyurea in patients with Polycythemia Vera [PROUD-PV study]), as well as additional clinical studies. Also, the Sponsor plans to provide status update to the Agency on the clinical program progress and to obtain concurrence and guidance from FDA on the adequacy of the clinical data to support BLA filing.

FDA sent Preliminary Comments to PharmaEssentia on April 17, 2017.

2. DISCUSSION

Preamble:
The Agency has significant concerns with your proposed BLA submission. The PROUD-PV trial results may not be adequate to support a favorable regulatory decision. We recommend that you conduct a new trial to support the use of Ropeginterferon alpha-2b in patients with polycythemia vera. The Agency would be willing to discuss appropriate trial design with you in future meetings. Specific deficiencies are outlined below:

- You amended the protocol and statistical analysis plan to change the primary endpoint from a superiority to a non-inferiority design after enrollment was complete. The Agency did not agree to a non-inferiority design and has concerns with the statistical assumptions. See the FDA Response to Question 3.

- In the previous Type B Pre-IND meeting held with the Agency on September 26, 2013, the primary endpoint of complete response with demonstration of durability was discussed. While the endpoint of complete response (defined by complete hematologic response and normalization of spleen size) may be adequate, it is not acceptable to change the endpoint to one based on laboratory parameters only. Additionally, any endpoint ultimately selected will need to be supported by the literature as clinically meaningful. See the FDA Response to Question 1.

- As noted in your briefing document, you are concerned that the trial population included a majority of patients that had a normal spleen at baseline. Additionally, your patient population allowed entry of patients that were already receiving hydroxyurea. Inclusion of patients on hydroxyurea may have limited your ability to demonstrate the treatment effect of your product as compared to that of hydroxyurea. When selecting a patient population for trial participation, the population should have severe enough symptomatology to allow you to demonstrate an improvement with use of the drug.

- We have additional concerns regarding the Ropeginterferon alpha-2b starting dose and dose titration methods. Refer to the additional Clinical Pharmacology Comments.

Question 1: *Does the Agency agree* (b) (4)

FDA Response to Question 1: No. (b) (4)

Discussion: There was no discussion.

Question 2: *Does the Agency agree* (b) (4)

FDA Response to Question 2: No, it is not appropriate for the Agency to comment on the findings from safety data at this stage.

Question 2: *Does the Agency agree that the protocol (study design) and Statistical Analysis Plan (SAP and subsequent amendments) submitted to the European Agency (EMA) support a claim of non-inferiority for P1101 compared to HU for the primary treatment of PV in regard to the primary endpoint of durable response (with and without consideration of spleen size)?*

Discussion: There was no discussion.

FDA Response to Question 3: No. The study was originally designed to demonstrate superiority of P1101 compared to HU. The protocol amendment of this open-label trial, dated on June 15, 2016, changed the superiority design to a non-inferiority design and the change was made more than 12 months after the completion of the last enrollment (May 13, 2015), when the primary endpoints were measured for all subjects. There were no pre-specified non-inferiority analyses as well as no agreed non-inferiority margin.

In addition, we have the following concerns about the rationale you provided for your proposed non-inferiority margin. The margin is derived based on an assumed control effect rate of 25%, for which you did not provide justification. It is unclear why it is different from the rate of 15% you originally assumed for the control arm. The major difference between this assumed rate and the observed rate of 46% in the trial also raises concerns of constancy assumption violation. Please also be advised that, even if the trial is well designed with pre-specified analysis, one single non-inferiority study may not be sufficient to support a licensure.

Additionally, the Agency does not agree to the removal of spleen size from the definition of durable response. See FDA Response to Question 1 and the Preamble.

Discussion: There was no discussion.

Question 4: (b) (4)

FDA Response to Question 4: No. (b) (4)

Discussion: There was no discussion.

Additional clinical pharmacology comments

You should gather and submit the current available data to conduct population PK analysis, ER analyses of PD markers, efficacy and safety to justify the proposed starting dose and dose titration and provide a rationale for your approach. The analyses should address the questions including (but not limited to):

1) What is the most appropriate starting dose?

2) What is the most appropriate titration schedule?

3) Should a patient-specific starting dose or dose titration be selected based on patients' baseline information?

Discussion: There was no discussion.

Meeting Discussion:

The Agency reiterated their concerns with the PROUD-PV study as outlined in the Preamble and relevant sections of the preliminary FDA responses. The Agency explained that the issues with the PROUD-PV study limit the ability to draw meaningful conclusions regarding the efficacy and activity of P1101. The Agency recommended that future meetings be held to discuss a subsequent trial and obtain Agency input on trial design. The Agency reiterated their recommendation that subsequent trials should enroll a more symptomatic and/or more refractory patient population to allow the sponsor to demonstrate a benefit with their product. Additionally, the sponsor will need to provide evidence that their chosen endpoint is a measure or surrogate of clinical benefit. In this regard, the Agency noted that in addition to durable improvement in hematologic laboratory parameters, the current guidelines for disease response in polycythemia vera also require symptom improvement, absence of hemorrhagic/thrombotic events and resolution of splenomegaly. The Agency stated that further discussion would be needed to reach agreement on an appropriate clinical trial endpoint, patient population, and trial design. The sponsor stated that they will request subsequent meetings to discuss a path forward for the development of P1101.

3.0 OTHER MEETING INFORMATION

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 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

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* 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.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards 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. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.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 the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. 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.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

There are no attachments or handouts.

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
04/21/2017