

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214375Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

NDA 214375

MEETING MINUTES

Polarean Inc.
Attention: Jason Mercer, PhD, RAC
Authorized US Agent
Product Development Champion
c/o Facet Life Sciences
215 E Deer Run
Durham, NC 27523

Dear Dr. Mercer:¹

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xenoview (xenon-129 hyperpolarized) for Inhalation.

We also refer to your October 22, 2021, correspondence requesting a meeting to discuss the specific information needed to address the issues identified in the Complete Response Letter dated October 05, 2021.

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 me, at 301-796-2219.

Sincerely,

{See appended electronic signature page}

August Hofling, MD, PhD
Clinical Team Leader
Division of Imaging and Radiation Medicine
Office of Specialty Medicine
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: A
Meeting Category: Guidance

Meeting Date and Time: November 19, 2021 from 2:00 pm to 2:30 pm E.S.T.
Meeting Location: Teleconference

Application Number: NDA 214375
Product Name: Xenoview (xenon-129 hyperpolarized) for Inhalation.
Indication: For use with magnetic resonance imaging (MRI) (b) (4)

Applicant Name: Polarean, Inc.
Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetics Act

Meeting Chair: August Hofling, MD, PhD, Clinical Team Leader
Meeting Recorder: Lisa Skarupa

FDA ATTENDEES

Charles Ganley, MD, Director, OSM
Alexander Gorovets, MD, Deputy Director, OSM
Libero Marzella, MD, PhD, Director, DIRM
August Hofling, MD, PhD, Clinical Team Leader, DIRM
Brenda Ye, MD, Medical Officer, DIRM
Brian Booth, PhD, Office of Clinical Pharmacology, Division Director, DCPI
Sriram Subramaniam, PhD, Office of Clinical Pharmacology, Reviewer, DCPI
Danae Christodoulou, PhD, Branch Chief, OPQ, DNDPIII
Eldon Leutzinger, PhD, CMC Team Leader, OPQ, DNDPIII
Vidya Pai, PhD, Branch Chief, CDER, OPQ, OPMA
Ningzhi Li, PhD, Biomedical Engineer, CDRH, OPEQ, OHT7, DRH, MREPB
Dan Krainak, PhD, Device Team Lead, CDRH, OPEQ, OHT7, DRH, MREPB
LT Nam To, Biomedical Engineer, CDRH, OPEQ, DRP1
Jagjit Grewal, Regulatory Policy Advisor, OND, ONDP, DRP
Lisa Skarupa, Senior Regulatory Project Manager, DIRM

SPONSOR ATTENDEES

Richard Hullihen, Chief Executive Officer, Polarean
Kiarash Emami, PhD, VP Technology and Applications
Neil Wadehra, VP Operations, Polarean
Alex Dusek, VP Commercialization, Polarean
(b) (4) Consultant, Polarean

Bastiaan Driehuys, PhD, Chief Technology Officer, Polarean

(b) (4) Medical Device Regulatory Consultant, (b) (4)

(b) (4) Medical Device Quality Consultant, (b) (4)

(b) (4) Regulatory Consultant, Facet Life Sciences

1.0 BACKGROUND

On October 22, 2021, Polarean requested a meeting to discuss the specific information needed to address the issues identified in the Complete Response Letter issued to them on October 05, 2021; the submission included the meeting package. On November 8, 2021, a revised briefing package was received. The Preliminary Comments were sent November 16, 2021.

2.0 DISCUSSION

2.1 Chemistry, Manufacturing and Controls

Question 1 *Does the Agency agree, as advised during the May 2015 Type C Meeting, that for the purpose of finished pharmaceutical cGMPs, that the drug product that is manufactured and released is the Xe, He, N2 gas blend (packaged in multi-dose high pressure aluminum cylinders)?*

FDA Response to Question 1:

Refer to the combined response for Questions 1 and 2 below.

Question 2 *Does the Agency agree with Polarean's position that the quality and purity of hyperpolarized xenon-129 gas is assured by application of cGMPs to the Xe, He, N2 gas blend (packaged and distributed to hospitals in multi-dose high pressure aluminum cylinders), and through the design and performance controls on the Xenon Hyperpolarizer and Polarization Measurement Station, that, together, produce the final hyperpolarized xenon-129 dose administered to the patient in the flexible Dose Delivery Bag?*

FDA Response to Questions 1 and 2:

Yes, we agree that for the purpose of finished pharmaceutical cGMPs, the production of the gaseous blend of Xe, He, N2 under GMP (b) (4) is acceptable; however, the Agency will be approving the final medical product (Xe-129 hyperpolarized) for patient administration based on the demonstrated performance of the Hyperpolarizer through device validation studies and/or review of the (b) (4) XenoView

Operator's manual, device design, and design controls. We are requesting additional documents to make our assessments of the final medical product as listed below:

- a. Submit an approved protocol with details on the manufacturing steps, process controls, acceptance criteria of the drug/device quality attributes, and performance, with approval by Quality personnel under the Polarean Quality System.**
- b. Submit a completed validation report for the clinical batches (b) (4) of the Hyperpolarizer as proposed, with details on actual yields from a minimum of three batches that demonstrate dose equivalent requirements have been met.**
- c. Submit the benchmark verification doses conducted (b) (4) along with the procedure/SOP.**

Meeting Discussion

Sub-bullet 'c' above was the focus of discussion. Polarean indicated the benchmark verification (b) (4)

The results would be reflective of conditions provided in Table 2 of the meeting package. The Agency did not have concerns with this general approach though the specific calculations regarding dosing had not been verified at the time of the meeting. Additional procedural controls at the user site would be available as components of a protocol within sub-bullet 'a'.

Additional post-meeting comment:

Polarean had proposed that a dose equivalent (DE) of (b) (4) mL is the minimum acceptable level. FDA recommends a specification for the minimum acceptable DE of ≥ 75 mL. Please ensure that the validation protocols discussed above account for a minimum requirement of $DE \geq 75$ mL.

2.2 Drug Substance and Drug Product

Question 3 Does the Agency agree that the proposed information will satisfy the request for information on hyperpolarized xenon-129 produced for clinical use and by the Hyperpolarizer device (b) (4)

FDA Response to Question 3:

We agree with your proposal to generate the same data for Xe-129 hyperpolarized as for the clinical batches (b) (4) of the device (Hyperpolarizer). Please submit a table (side by side comparison) of the results of the clinical versus commercial batches in the resubmission.

Question 4 Does the Agency agree with the proposed approach to validate the hyperpolarized 129-xenon production method with the Hyperpolarizer (b) (4) and 3 batches of gas blend manufactured (b) (4)

FDA Response to Question 4:

Yes, we agree with the approach of validation using three batches of gas blend (b) (4) implements GMP updates to their quality system and by using the device (Hyperpolarizer) (b) (4)

Meeting Discussion

The Applicant stated that for timing purposes, they will perform validation (b) (4)

The Applicant noted (b) (4)

. The Agency agreed with the approach.

In addition, Polarean pointed out (b) (4)

Additional post-meeting comment:

Polarean submitted Verbal Observation 4 and related response for comment and discussion on the day of the meeting. As (b) (4) was not part of the meeting, no detailed discussions on GMP gaps related to stability were possible.

However, as noted in the Agency's response, the validation of Hyperpolarizer (b) (4) with three batches of gas blend (b) (4) implements GMP

updates is acceptable. Similarly, the stability assessment of three batches of gas blend manufactured after (b) (4) implements GMP updates to meet quality system requirements around stability programs and testing under cGMP is acceptable. An approved protocol, short and long-term stability report, and the quality procedures are expected to be in place prior to resubmission of the NDA application. We encourage Polarean to work closely with (b) (4) to address any identified inspectional and post action concerns communicated by the Agency in the EIR (Establishment Inspection Report) and Post Action Letter. A meeting request for (b) (4) GMP concerns could be accommodated with both parties.

Question 5 *Does the Agency agree that Polarized 129-Xe DE per volume of gas in a prepared dose (e.g. range of DE/1000 mL) is an acceptable unit of measure of strength of xenon-129 hyperpolarized?*

FDA Response to Question 5:

We acknowledge your approach, and we understand that the strength will be expressed as a percentage of volume per volume. We also acknowledge that your calculation of DE takes into account the isotopic enrichment of Xe-129 and degree of polarization. We will evaluate your proposal at the time of resubmission. We remind you that “strength” is a quality attribute and needs to include isotopic enrichment and degree of polarization. In general dose calculations are proportional to strength.

Meeting Discussion

The Applicant and Agency agreed to revisit strength determination during review of the resubmission.

2.3 Regulatory and Procedure

Question 6 *Given that the anticipated responses to the CRL will be primarily clarifying regulatory definitions for the drug substance and drug product along with minor re-analysis of data previously submitted to the application, does the Agency agree that the resubmission can be classified as a Class 1 resubmission?*

FDA Response to Question 6:

No, the resubmission will be classified as Class 2 due to reevaluation of the manufacturing sites before approval of the application, which may require pre-approval inspections.

Additional CMC comment:

In your application, you stated that the in-use period for Xe-129 hyperpolarized is about 60 minutes. Please verify the in-use period with the three batches of Xe-129 hyperpolarized when you validate (b) (4)

3.0**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 Information² and Pregnancy and Lactation Labeling Final Rule³ websites, which include:

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant

² <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

³ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

An excerpt from the establishment inspection report sent to (b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AUGUST A HOFLING
12/16/2021 02:46:15 PM



IND 75010

MEETING MINUTES

Facet Life Sciences, Inc.
c/o Polarean, Inc.
Attention: Jason Mercer, PhD, RAC
Sponsor's Authorized Representative
215 E. Deer Run
Apex, NC 27523

Dear Dr. Mercer:

Please refer to your pre-investigational new drug application (PIND) file for Xenon 129, NC 100674 inhalation.

We also refer to the meeting between representatives of your firm and the FDA on May 4, 2020. The purpose of the meeting was to discuss We also refer to your March 3, 2020, correspondence requesting a to discuss the content and format of your upcoming 505(b)(2) NDA submission.

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 Ms. Sharon Thomas, Regulatory Project Manager at 301-796-1994.

Sincerely,

{See appended electronic signature page}

Louis Marzella, MD, PhD
Director
Division of Imaging and Radiation Medicine
Office of Specialty Medicine
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA
Meeting Date and Time: Monday, May 4, 2020, 4:00 p.m. – 5:30 p.m.
Application Number: IND 75,010
Product Name: Hyperpolarized 129-Xe
Indication: For use with MRI (b) (4)
Sponsor's Name: Polarean Inc.

FDA ATTENDEES

Division of Imaging and Radiation Medicine

Libero Marzella, MD, PhD, Division Director
Brenda Ye, MD, PhD, Clinical Reviewer
Ira Krefting, MD, Safety Director
August Hofling, MD, PhD, Clinical Team Leader
Alex Gorovets, MD, Deputy, Division Director
Jonathan Cohen, PhD, Toxicology Reviewer
Christy John, PhD, Clinical Pharmacology Team Leader, DCPV
Sue-Jane Wang, PhD, Deputy Director (acting), DBI / Statistics
Jyoti Zalkikar, PhD, Secondary Statistical Reviewer, DBI
Xiaomin Zhang, PhD, Statistical Reviewer, DBI
Chris Galliford, PhD, CMC Reviewer
Eldon Leutzinger, PhD, CMC Team Leader
Danae Christodoulou, PhD, CMC Supervisor

Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine

John Alexander, M.D. Deputy Director
Shetarra Walker, M.D. Pediatric Team Leader (Acting)
Rosemary Addy, M.H.S. Supervisory Consumer Safety Officer
Meshaun Payne, MHCA, Senior Regulatory Project Manager

Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis

Ebony Whaley, PharmD, Safety Evaluator, DMEPA

Devin Kane, PharmD, Safety Evaluator, DMEPA
Hina Mehta, PharmD, Team Leader, DMEPA
Lolita White, PharmD, Human Factors Team Leader, DMEPA
Mishale Mistry, PharmD, Associate Director for Nomenclature and Labeling, DMEPA

SPONSOR ATTENDEES

Richard Hullihen – Chief Executive Officer
Kenneth West – Chief Operating Officer
Bastiaan Driehuys, PhD – Chief Technical Officer
Kiarash Emami, PhD – V.P. Technology and Applications
Neil Wadehra – V.P. Operations
Alex Dusek – V.P. Commercialization
Keavy Isaacs – Project Manger
(b) (4) Medical Device Regulatory Consultant (b) (4)
(b) (4) Regulatory Consultant (Facet Life Sciences)

1.0 BACKGROUND

The Sponsor is developing a drug/device combination to produce and administer hyperpolarized ^{129}Xe gas as a diagnostic agent used in conjunction with magnetic resonance imaging (MRI) (b) (4)

(b) (4) The Sponsor submitted this pre-NDA meeting request on March 3, 2020 to discuss the format and content of the upcoming 505(b)(2) NDA submission. FDA provided preliminary comments on April 29, 2020. The Sponsor decided to proceed with the meeting to discuss questions 6, 8, 9, 10, 12, and 17-19.

2.0 DISCUSSION

Following introductions, discussion ensued with the Sponsor's power point presentation (Attachment A). The Sponsor's questions are in italics; FDA's response is in bold and the meeting discussion is in indicated in ***bold italics*** below.

Clinical Questions

Question 1.

Does the Agency agree that the results from clinical studies POL-Xe-001 and POL-Xe-002 provide adequate evidence that the efficacy of Hyperpolarized ^{129}Xe gas for use with MRI (b) (4) is equivalent to the reference product, Xenon Xe-133 (NDA 017284) and no additional studies are needed to support an NDA?

FDA Response to Question 1.

We agree that no additional studies are required for NDA submission. As discussed during our teleconference on 12/19/19, we anticipate results of the proposed

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Silver Spring, MD 20993
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exploratory analyses to be included in the NDA submission for review. We view studies POL-Xe-001 and POL-Xe-002 to be most critical for efficacy evaluation with the proposed published literature as only potentially supportive of efficacy.

Question 2.

Does the Agency agree that the available safety data from clinical studies POL-Xe-001 (N=34), POL-Xe-002 (N=49), and GE-141-001 (N=44) along with safety data described in the clinical literature provide adequate evidence of the safety of Hyperpolarized ¹²⁹Xe gas for use with MRI (b) (4) and no additional studies are needed to support an NDA?

FDA Response to Question 2.

We find your proposed safety population to be relatively small. We recommend including patients from Study POL-Xe-003 and any other trials you conducted if safety data were collected in them. We request an explanation for the apparent difference between safety profiles in the GE-141-011 study and the POL-Xe-001 and POL-Xe-002 studies. For published studies that use a formulation of hyperpolarized ¹²⁹Xe that differs from your product, a justification (i.e., bridging) for reliance on the reported safety data will be needed.

Question 3.

Does the Agency agree that a side-by-side presentation of the efficacy data from the Phase 3 studies is acceptable and that data pooling is not necessary?

FDA Response to Question 3.

We agree that you do not need to pool efficacy data from the two Phase 3 studies. However, an integrated summary of efficacy is still required for NDA filing.

Question 4.

Polarean intends to present both side-by-side presentation and pooled safety data for the Phase 3 studies. Does the Agency agree with this approach?

FDA Response to Question 4.

We recommend presenting pooled and side-by-side safety data from the two Phase 3 studies, the Phase 1 study (GE-141-001), and any available safety data from Study POL-Xe-003 and other trials you may have conducted. From this clinical trial safety database, we recommend additional presentation of safety results based on total xenon gas dose administered.

Additionally, we recommend presentation of available safety data from the literature on a per-publication and pooled basis. Adult and pediatric safety data from the published data should be presented separately. We note that certain publications that you consider to be supportive of efficacy also appear to contain safety data.

We also note that an integrated summary of safety is required in the NDA.

Pharmacokinetic Data

Question 5.

Does the Agency agree that the clinical pharmacology data are acceptable for use in the product labeling?

FDA Response to Question 5.

We agree that the clinical pharmacology data are adequate for the use in product labeling.

Question 6.

Are there other aspects of the clinical sections of the NDA the FDA would like to comment on or that Polarean should take into consideration?

FDA Response to Question 6.

- 1) For your phase 3 studies, indicate the disease that led to lung resection or lung transplant in each patient. Also describe the type of surgery each patient underwent (e.g., left upper lobectomy, bilateral lung transplant).
- 2) For Study POL-Xe-001, include the preoperative FEV₁ and DLCO for each patient, if collected.
- 3) From a statistical analysis perspective, we advise that you provide the following results for each phase 3 study in your NDA:
 - Provide analysis results similar to the summary in Table 4 in your meeting background material but broken down by randomization group
 - You need to demonstrate that the order that a subject received (¹²⁹Xe then ¹³³Xe or “¹³³Xe then ¹²⁹Xe”) does not affect the within-subject difference, therefore it does not substantially affect the primary endpoint evaluation or by-zone evaluations. For example, you may construct a statistical model to account for the order and derive the interval estimates from the model. If you take this approach, you should assess the goodness of fit of the model used.
 - Provide the stratified analysis (stratified by randomization group) of the primary endpoint and the by-zone endpoints to support your primary and secondary analyses.
- 4) Include each clinical site and contact information in the NDA for clinical inspection. See OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS at the end of the letter.

- 5) We find study drug dosing described in the meeting package confusing. For example, the meeting package reports that “Up to 750 mL of (b) (4) 129Xe gas diluted to 1 L total with Nitrogen gas, NF (99.999% purity) was administered from the Dose Delivery Bag by instructing the patient to inhale the entire bag contents”. But in fact, the 750 mL appears to be xenon gas, (b) (4) We request that you report accurate study drug dosing in the NDA.
- 6) Subgroup analyses based on age, gender, and race for both efficacy and safety should be included in the NDA.
- Provide subgroup analyses on the primary efficacy endpoints by age, gender, and race for each phase 3 study.
 - Provide subgroup analyses of adverse events by age, gender, and race for the entire safety population including any available safety populations from the literature.
- 7) Submit the coding dictionary (e.g., MedDRA version) used for mapping investigator verbatim terms to preferred terms.

Meeting Discussion for Question 6.

Polarean asked the Agency to expand on the reason for the request in item 1. The Agency stated that they are interested in characteristics of the population studied. Polarean stated that they did not collect information on the underlying disease that caused the patient to be evaluated for lung resection or transplant surgery. Polarean has done a preliminary review of the medical history of patients in these studies and has observed that patients’ respiratory illness background conditions included COPD, asthma, interstitial lung disease, pulmonary mass, and pulmonary hypertension. The Agency stated that they will be interested to see the data regarding medical history, similar to what Polarean presented in slide 11 of their presentation.

Polarean stated that only 40% of study patients went on to lung resection surgery in Study POL-Xe-001. The type of transplant in Study POL-Xe-002 was not captured.

Polarean acknowledged the typographical error in item 5.

Nonclinical Question

Question 7.

The nonclinical program is summarized in Section 10.2. Does FDA agree that the nonclinical program is adequate to support the NDA for the product for use with MRI (b) (4) and no additional nonclinical studies are needed?

FDA Response to Question 7.
We agree.

Chemistry, Manufacturing, and Controls Questions

Question 8.

Does the Agency agree with the approach for providing CMC information?

FDA Response to Question 8.

In general, your approach appears to be acceptable. The data provided in Module 3 will be reviewed in detail at the time of the NDA submission. In addition, please note that the CMC information provided should be for the drug product in the *final market presentation* of the drug. In particular, critical quality attributes such as the isotopic purity of the (b) (4) gas, the container/closure system, the degree of hyperpolarization should not differ significantly from those used in the pivotal clinical trials. In particular, stability data for the gas blend should be in the container/closure system intended for use with the marketed product and be complete at the time of submission. A strategy (b) (4) should also be provided on submission of the NDA.

Meeting Discussion for Question 8.

The Sponsor provided an overview of the manufacturing process

(b) (4)

(b) (4)

FDA reminded the Sponsor to provide information needed to bridge the

formulation of the drug product in the to-be-marketed presentation at the time of NDA submission.

FDA suggested that periodic quality tests on the gas blend may be needed to ensure stability. FDA inquired about the factors resulting in variability in the process. The Sponsor stated (b) (4)

Regarding FDA's request for the "stability data for batches of the gas stored in the container/closure system intended for the marketed product." the Sponsor stated they were conducting a stability study with the gas blend stored in aluminum cylinders and agreed to provide the stability data in the NDA.

Question 9.

(b) (4) ***¹²⁹Xe gas and ¹²⁹Xe/He/N₂ gas blend are manufactured in accordance with the Agency's Guidance for Industry: Current Good Manufacturing Practice for Medical Gases. Are there any specific aspects of the manufacturing process that the Agency would like for Polarean and (b) (4) to consider when preparing the NDA and DMF?***

FDA Response to Question 9.

In general, the approach presented in the meeting package appears to be acceptable. Additional considerations include, but are not limited to, the following:

A DMF submitted for (b) (4) ¹²⁹Xe gas and ¹²⁹Xe/He/N₂ gas blend should include a detailed description of the manufacturing process including the source and purity of each gas. Information about the supply chain for each gas, as well as the acceptance criteria at the DMF holder's manufacturing facility should also be included. The DMF should contain a summary of representative batch data as well as the raw analytical data generated from the quality tests. In addition, the isotopic purity of the ¹²⁹Xe is a critical quality attribute and should be a release criterion for each batch of gas or gas blend. A complete description of the container/closure system should be included, as well as stability data for batches of the gas stored in the container/closure system intended for the marketed product.

Studies should be included that demonstrate that use (and potential re-use) of gas cylinders does not result in corrosion and the introduction of foreign particulates of leachable substances into the gas blend. With this in mind, an appropriate expiration period and storage information for each container of the gas should also be included.

Meeting Discussion for Question 9.

The Sponsor discussed details of the manufacturing process and maintenance program. FDA stated that it was a reasonable approach based on the risk analysis.

FDA will provide further comments on the extractable components of the gas blend cylinder.

Post-meeting comment for Question 9.

(b) (4)
This will be an NDA review issue.

Question 10.

Does the Division find the proposed commercial drug product specification adequate to support the NDA (refer to Error! Reference source not found.)?

FDA Response to Question 10.

In general, the provided drug product specification appears to be adequate to support the NDA. However, we note that the specification for isotopic enrichment of ^{129}Xe is NLT than 80%, which introduces a quality concern that varying degrees of hyperpolarization may be observed if lots of gas with substantially different levels of isotopic enrichment are used. You should use a specification for isotopic enrichment that is in line with ^{129}Xe gas used in the pivotal clinical trials. This will be a review issue at the time of NDA submission, and may make it difficult to compare data obtained from the batches used in clinical trials to the intended marketed presentation if the degree of isotopic enrichment varies significantly.

Meeting Discussion for Question 10.

See Discussion points for Question 8 and 9.

Device Questions

Question 11.

We propose to include the device-specific portions of the application in Section 3.2.R. A table of contents with the proposed device section structure will be included in the briefing package. Does the Agency have any comments regarding the Device specific portion of the NDA or Device content locations based on the table of contents that has been provided?

FDA Response to Question 11.

In addition to the device specific content proposed, we expect the draft labeling section (009) to include the following:

- a. any user guide labeling,
- b. any training materials,

- c. any training requirements for operators, and
- d. any site planning information.

Question 12.

On 10 June 2019, Polarean submitted a meeting package for a Type C, Guidance meeting request to discuss the drug/device combination product. Polarean included the results of a risk assessment for the device system and a formative human factors study. Polarean's conclusion from the risk assessment and formative human factors study is that a summative human factors study is not necessary. The Agency stated in their response on 03 July 2019 that the Agency would respond in writing within 60 days if the Agency concurred with Polarean's determination. Polarean has not yet received a response on this issue. Does the Agency agree with Polarean's determination that no additional human factors validation studies are needed?

FDA Response to Question 12.

Our review is ongoing. We refer to the Agency's April 24, 2020, Information Request (IR) in which we requested additional information regarding your proposed product's device components, cheat sheet labeling, and the intended user training. Once we have completed our review, we will provide a written response.

Meeting Discussion for Question 12.

Polarean summarized their lengthy communications with FDA regarding Polarean's risk analysis for the product and the potential need for a human factors study. Polarean is concerned about the implications for the NDA submission. FDA explained that Polarean's latest responses are under review and committed to providing additional comments in the official meeting minutes.

Post-Meeting Comment for Question 12.

Based on the review of Polarean's use-related risk analysis (URRA) and formative human factors (HF) data, FDA has determined that no additional HF data are needed to support the NDA. However, if additional changes are made to the user interface prior to submitting the NDA, additional HF considerations may apply. The final acceptability of the labels and labeling will be determined once the NDA is submitted for Agency review.

Question 13.

(b) (4)

(b) (4)

FDA Response to Question 13.

(b) (4)

Regulatory and Procedural Questions

Question 14.

Does the Agency agree with the “dose equivalent” unit of measure as proposed in the draft prescribing information?

FDA Response to Question 14.

See FDA response to Questions 8-10.

Question 15.

Polarean intends to file a 505(b)(2) NDA referencing the Agency's previous determination of efficacy and safety for Xenon Xe-133 Gas Inhalation (NDA 017284) for evaluation of pulmonary function and for imaging the lungs. Does the Agency agree that the 505(b)(2) pathway is appropriate?

FDA Response to Question 15.

For your proposed NDA, we do not anticipate reliance on FDA's previous determination of efficacy and safety for 133Xe. However, the anticipated value of safety data from your proposed published literature support still makes the 505(b)(2) pathway appropriate.

Question 16.

Polarean will describe proposed naming of the device components, ¹²⁹Xe gas blend, and Hyperpolarized ¹²⁹Xe Gas in the briefing package. Does the Agency agree with Polarean's proposed naming structure?

FDA Response to Question 16.

We note the use of a product name, Xenoview, in the Briefing Document for IND 75010. If you intend to have a proprietary name for your product, we recommend you submit your request for FDA review of your proposed proprietary name during the IND phase of your drug development program. The content requirements for such a submission can be found in the Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>.

Assuming your question also refers to device names in your draft labeling, we have no concerns at this time.

Question 17.

A draft of the proposed prescribing information will be included in the briefing package. Does the Agency have any comments on the draft proposed prescribing information or specific advice for issues that should be addressed in the NDA to support the prescribing information as proposed?

FDA Response to Question 17.

It is premature to comment on labeling at this point. Similarly, the wording of the indications statement will be subject to review of the complete NDA.

Meeting Discussion for Question 17.

Polarean asked FDA to comment on the proposed indication statement. The Agency stated the wording will be subject to review of the complete NDA.

FDA stated that the indication is generally dependent on the population studied in the efficacy trials. The proposed indication is (b) (4)
(b) (4) FDA pointed out (b) (4)

Question 18.

The pediatric study plan for Hyperpolarized ^{129}Xe gas has been agreed upon with the Agency. Polarean intends to submit a request for deferral of pediatric studies with the NDA. Does the Agency agree that a deferral of pediatric studies is appropriate?

FDA Response to Question 18.

The Agency is still in agreement with the plan as outlined in the Agreed iPSP on November 2, 2016 and included within the Agreement letter dated December 5, 2016.

The Agreed iPSP stated the pediatric protocol would be submitted by 1Q2020. Please provide us with an update on the current status of your pediatric development plan.

Meeting Discussion for Question 18.

Polarean stated that their original agreed iPSP timeline included submission of an NDA in 2Q 2018 followed by submission of the pediatric protocol for review in 1Q 2020. The product development program has been delayed hence the delay in submission of the pediatric protocol.

Since the iPSP agreement, Polarean has realized that the proposed pediatric study is infeasible (b) (4)

The revised PSP would be submitted in June. FDA stated that further comments will be provided in the post-meeting minutes.

Post-Meeting Comment for Question 18.

FDA recommends against revision of the current Agreed iPSP at this time. FDA requests further description of the newly proposed pediatric study in patients (b) (4)

In addition, FDA asks that the Sponsor provide information about how the condition being studied in adults is related to the condition they intend to study in pediatric patients, i.e. would these data support a similar claim for both populations.

Question 19.

Does FDA have any additional guidance or suggestions on any aspect of the development program or NDA?

FDA Response to Question 19.

- a) Given that your proposed product is novel and complex with multiple drug/device components, we suggest you consider giving a presentation/demonstration at the Applicant Orientation Meeting, perhaps with a combination of video and/or device (parts) as well as sample diagnostic images.
- b) The procedure utilized by the device to produce the hyperpolarized Xenon is complex enough to introduce potential use errors and will require a detailed training program for operating your device. We suggest that you examine the potential for partially or fully automating the hyperpolarizer device. The technology for automating this device, for instance, automated solenoid valves, pressure regulators, and programmable logic controllers is readily available and robust.

Meeting Discussion for Question 19.

Polarean agreed with the FDA's suggestion for more in-depth presentation at the Applicant orientation meeting.

3.0. OTHER IMPORTANT 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*.¹ 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 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.

¹ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

² <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

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 Applicants³ 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

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.⁵

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data*. This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,⁶ as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page⁷ 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.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled

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 <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

⁶ <https://www.fda.gov/media/88173/download>

⁷ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

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 started on or 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 FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.⁸ For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide⁹ (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.¹⁰ When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission. Additional information can be found at FDA.gov.¹¹

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

⁸ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

⁹ <https://www.fda.gov/media/88173/download>

¹⁰ <https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

¹¹ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

- There were no additional issues identified that required further discussion.

5.0 ACTION ITEMS

- No issues have been identified that require further actions.

6.0 ATTACHMENTS AND HANDOUTS

- ATTACHMENT A (Sponsor’s slides)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LIBERO L MARZELLA
06/03/2020 06:24:38 PM



IND 075010

**MEETING REQUEST-
WRITTEN RESPONSES**

Polarean, Inc.
Attention: Kenneth West
CEO
P.O. Box 14805
Research Triangle Park, NC 27709-4805

Dear Mr. West:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Xenon 129, NC 100674 inhalation.

We also refer to your submission dated June 8, 2016, containing a Type C meeting request. The purpose of the requested meeting was to discuss 2 phase 3 synopses.

Further reference is made to our Meeting Granted letter dated June 20, 2016, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your June 8, 2016 background package.

If you have any questions, call me at (301) 796-3908.

Sincerely,

{See appended electronic signature page}

Alberta Davis-Warren
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Written Responses



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

WRITTEN RESPONSES

Meeting Type: Type C

Meeting Category: Guidance

Application Number: IND 75010

Product Name: Xenon 129, NC 100674 inhalation

Proposed Indication: Diagnostic (b) (4)
(b) (4)

Sponsor/Applicant Name: Polarean, Inc.

Regulatory Pathway: 505(b)(1)

1.0 BACKGROUND

On June 8, 2016, Polarean, Inc. submitted a meeting request to the Division of Medical Imaging Products to request feedback on two proposed Phase 3 studies for Xenon 129, NC 100674, inhalation. Specifically, as stated in the sponsor's meeting package, the sponsor wants to address the following objectives:

- Obtain Agency feedback on the 2 proposed Phase 3 studies; 1 to evaluate patients being considered for lung resection surgery and 1 to evaluate patients being considered for lung transplantation, and
- Obtain Agency agreement that the Phase 3 program supports the indication

(b) (4)

The June 8th meeting package emanates from discussions held during the EOP2 meeting on March 3, 2016. On the basis of the EOP2 meeting, the sponsor has submitted updated protocol synopses of their two Phase 3 studies along with questions pertaining to the drug development program for Xenon 129 for FDA review and comments.

2.0 QUESTIONS AND RESPONSES

We have reviewed the meeting package submitted on June 8, 2016, and provide the following comments and responses to your questions.

Introductory Comments

We appreciate your efforts to develop Xenon-129 for performing pulmonary MRI imaging. Please see our below comments and recommendations.

Question 1:

The proposed Phase 3 study is an open-label study designed to evaluate the equivalence of ^{129}Xe MRI and ^{133}Xe Scintigraphy in patients being evaluated for possible lung resection surgery. Does FDA have any comments regarding the adequacy of the study design, specifically:

- a) Patient population;
- b) Sample size;
- c) Comparator;
- d) Efficacy assessments;
- e) Safety assessments, or
- f) Statistical methods?

FDA Response to Question 1:

Regarding the adequacy of the study design, we have the following comments and requests:

- **We note your proposed indication statement may need revision based on the patient populations evaluated in the Phase 3 studies and the clinical data used in support of your indications.**
- **We acknowledge there appears to be clinical value in estimating the post-operative FEV1 using imaging as part of the equation and that the data obtained from your proposed studies** (b) (4) **However, we would like to understand how the post-operative FEV1 estimates are calculated. Please provide a detailed description of how the estimated post-operative FEV1 is derived and include a mock calculation as an example.**

We recommend you include post-operative FEV1 obtained by spirometry as a reference standard for the estimates derived by Xenon-133 and Xenon-129 imaging, if possible. Please comment on how you might incorporate the reference standard (FEV1 by spirometry) into your statistical analysis plan.

- **Please clearly identify the 6 lung zones proposed for the activity analysis.**
- **See Statistical Comments in our response for question 5.**

Question 2:

The proposed Phase 3 study is an open-label study designed to evaluate the equivalence of ^{129}Xe MRI to ^{133}Xe Scintigraphy in patients being evaluated for possible lung transplant surgery. Does FDA have any comments regarding the adequacy of the study design, specifically:

- a) Patient population;
- b) Sample size;
- c) Comparator;
- d) Efficacy assessments;
- e) Safety assessments, or
- f) Statistical methods?

FDA Response to Question 2:

Please provide detailed information on how the information obtained from imaging is used in surgical planning in the lung transplant population.

We note the primary endpoint appears acceptable. However, we recommend region level (lung zones) comparisons also be conducted as part of the primary efficacy analysis; please revise the protocol accordingly.

Question 3:

Assuming the proposed Phase 3 prospective studies meet their primary efficacy objectives, does FDA agree that sufficient efficacy data would be available from the Phase 3 program, the GE-141-001 study, and the literature to support an NDA for the indication (b) (4)

FDA Response to Question 3:

It is premature to comment at this time. The adequacy of data obtained from your Phase 3 programs and the literature to support the proposed indication statement will be a review issue. We refer you to our above recommendations for revising the proposed Phase 3 study designs.

Question 4:

Assuming that the proposed Phase 3 prospective studies demonstrate adequate evidence of safety, does FDA agree that sufficient safety would be available from the Phase 3 program, the GE-141-001 study, and the literature to support an NDA for the indication (b) (4)

FDA Response to Question 4:

The plan to obtain adequate safety data to support an NDA submission appears reasonable.

Question 5:

What additional comments and advice does FDA have regarding the hyperpolarized ^{129}Xe gas Phase 3 program?

FDA Response to Question 5:

We have the following device, clinical-pharmacology, and statistical comments for your consideration:

Device comments:

- Please comment on the CDRH clearance status of the software that will be used for image quantification for both Xe-129 MRI and Xe-133 scintigraphy.

Clinical-Pharmacology comments:

- In response to your May 13, 2016, submission (follow-up to the End-of-Phase 2 meeting), we have the following comments:

1) We reiterate our recommendation that you identify near optimal dose and conditions (MR sequence, and acquisition parameters) prior to performing the Phase 3 studies.

2) We do not agree

(b) (4)

We continue to recommend that you acquire data on the exhalation, and absorption/plasma PK, of ^{129}Xe . In addition to providing information for the package insert, the timing of elimination will set a baseline for considering whether there is a need for dose adjustment for Specific Populations.

3) The topic of dosing of Specific Populations was not discussed at the End-of-Phase 2 meeting. Our expectation is that patients with altered lung function (e.g., COPD) might require dose adjustment. Please provide your strategy for acquiring data to address this issue, or scientific rationale that data is not needed.

Statistical comments:

- **Preliminary Note:** Two Protocols were submitted. Only the first of these will be covered in this Review. However, the statistic recommended by the Agency Reviewer covers both protocols.
- **Study Title:** Evaluation of Hyperpolarized ^{129}Xe MRI as compared to ^{133}Xe Scintigraphy for Assessment of Pulmonary Function in Patients being evaluated for Possible Lung Resection.

In this proposed Study ^{133}Xe Scintigraphy is positioned as the Control/Truth Standard for Evaluation of lung function, and ^{129}Xe MRI is the Test Diagnostic.

Patients who will (probably) undergo lung surgery will be assessed for FEV1.
(FEV1 = Forced expiratory Volume in one second)

Let FT(Pre) = Test Evaluation of Lung Function acquired Pre - Surgery
Let FT(Post) = Standard FEV1 acquired Post –Surgery

Likewise:

Let FC(Pre) = Control Evaluation of Lung Function acquired Pre - Surgery

Let FC(Post) = Standard FEV1 acquired Post - Surgery :

Both FT(Post) and FC(Post) are dependent of the portion of lungs remaining after surgery.

The Reviewer's understanding is that FT(Pre) and FC(Pre), as acquired here, are connected to inhalations and acquisition of images while the patient holds his/her breath. These procedures apparently are alternatives to Standard FEV1 for evaluation of lung viability, but have the added advantage of “imaging” lung areas. The Reviewer does not know if the imaging assessments impact surgery choices, but the statistical objectives stated below can be understood independently of such knowledge. The Sponsor's Primary Endpoint is the difference in Predicted Post- Surgery FEV1: Test Prediction minus Control Prediction (not actual Post-surgery FEV1). The precise manner in which this score is acquired is not necessary for discussion of the possible difficulties inherent in the Primary Statistical Objective, which will be stated and discussed below:

Statistics:

Set

PFT = Predicted FT(Post) ; PFC = Predicted FC(Post)

Set D = Mean Difference: PFT – PFC

Primary Objective: To show that: $-0.3 < D < +0.3$

This hypothesis will be tested through use of the mean difference:

D_s = Sample Mean PFT – Sample Mean PFC

One possible difficulty inherent in this objective is presented directly below in general terms rather than through samples, but the principal is the same, and suggests that the Objective might be too liberal. The mathematics is intended for the Sponsor's statisticians. The Reviewer's suggested alternative Primary Endpoint and Objective are provided under Proposed Alternative Primary Objective.

Mathematics:

Suppose the Objective is stated more generally: To demonstrate that: $-.D_1 < D < +D_1$

Let $PFT = PFC + D_0 + D_1 \eta$ with η a standard Normal and $D_0 < D_1$

Then: Mean Difference = $D_0 < D_1$, so the Objective is met

However, we can calculate for this model the probability that individual differences exceed D_1 :

$$P\{D > D_1\} > P\{\eta > 1 - D_0 / D_1\}$$

So, for instance, take $D_0 = .8D_1$ Then:

$$P\{D > D_1\} > P\{\eta > .2\} = .42$$

So:

Although the Mean Difference Objective is met, more than 40% of the patients will have The difference PFT - PFC in excess of the bound D_1

The Reviewer recommends that the Sponsor reconsider the Statistical Objective in order to account for the importance of individual patient differences in predicted scores. A possible approach is to focus the Primary Objective on the proportion of excessive differences (as explained below):

Proposed Alternative Primary Objective:

Let D_0 be some acceptable difference in Test Predicted FEV1 versus Control Predicted FEV1:

Let $PFT = \text{Predicted Test FEV1}$; $PFC = \text{Predicted Control FEV1}$

Let $D = PFT - PFC = \text{Difference in Predicted Values}$

Thus, the Statistical approach is:

For Patient K, let:

$X_K = 1$ if the Test Prediction is within D_0 of the Control Prediction ; $= 0$ Otherwise

$$\text{Let } S = (1/N) \sum_{K=1}^N X_K = \text{Sample Mean of the } X_K$$

Use S to test the Hypotheses:

$H_0: P \leq \alpha$ versus $H_1: P > \alpha$

Where P = Population Proportion of Successes (Cases where $X_K = 1$)

α = Acceptable Success Level

3.0 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 (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action. **We acknowledge the sponsor submitted an iPSP to FDA for review and comment on April 29, 2016.**

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

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/s/

ALBERTA E DAVIS WARREN
08/19/2016



IND 075010

MEETING MINUTES

Polarean, Inc.
Attention: Kenneth West
CEO
P.O. Box 14805
Research Triangle Park, NC 27709-4805

Dear Mr. West:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Xenon 129, NC 100674 inhalation.

We also refer to the meeting between representatives of your firm and the FDA on March 3, 2016. The purpose of the meeting was to discuss the Phase 3 program of your drug/device combination product.

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 me at (301) 796-3908.

Sincerely,

{See appended electronic signature page}

Alberta Davis-Warren
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: March 3, 2016, 4:00 PM–5:00 PM
Meeting Location: White Oak; Building 22; Conference Room 1315

Application Number: IND 075010
Product Name: Xenon 129
Indication: Hyperpolarized ¹²⁹Xe gas is a drug/device combination diagnostic agent for magnetic resonance imaging (MRI) of patients with suspected ventilation defects

Sponsor/Applicant Name: Polarean, Inc.

Meeting Chair: Libero Marzella, MD, PhD
Meeting Recorder: Alberta Davis-Warren

FDA ATTENDEES

Libero Marzella, MD, PhD, Director, DMIP
Alex Gorovets, MD, Deputy Director, DMIP (*by phone*)
Nushin Todd, MD, PhD, Clinical Team Leader, DMIP
Phillip Davis, MD, Medical Officer, DMIP
Michele Fedowitz, MD, Medical Officer, DMIP
Lydia Gilbert-McClain, MD, Deputy Director, DPARP
Eric Duffy, PhD, Director, DNDPII
Danae Christodoulou, PhD, Acting Branch Chief, DNDPII
Eldon Leutzinger, PhD, CMC Team Leader, DNDPII
Christopher Galliford, PhD, CMC Reviewer, DNDPII
Peggy Kriger, PhD, Microbiology Reviewer, DMA (*by phone*)
Gene Williams, PhD, Clinical Pharmacology Team Leader, DCPV
Christy John, PhD, Clinical Pharmacology Reviewer, DCPV
Thomas Gwise, PhD, Deputy Division Director, DBV (*by phone*)
Anthony Mucci, PhD, Statistical Reviewer, DBV
Jagjit Grewal, MPH, ADRA, ODEIV
Daniel Krainak, PhD, Biomedical Engineer, CDRH
Shannon Hoste, MSSE, MSM, RAC, Human Factor Pre-Market Evaluation, CDRH (*by phone*)
Patricia Love, MD, MBA, Deputy Director, OCP
James Bertram, PhD, Product Jurisdiction Officer, CDRH

Kristina Lauritsen, PhD, Product Jurisdiction Officer, CDER
Cherryn Chang, PharmD, Product Jurisdiction Officer, CDER *(by phone)*
Amy Taylor, MD, Medical Officer, DPMH
Matthew Bacho, Senior RPM, DPMH *(by phone)*
Yelena Maslov, PharmD, Team Leader, DMEPA *(by phone)*
Michelle Rutledge, PharmD, Safety Evaluator, DMEPA *(by phone)*
Alberta Davis-Warren, RPM, DMIP

SPONSOR ATTENDEES

Polarean:

Kenneth West, CEO
Bastiaan Driehuys, PhD, Chief Technology Officer
Neil Wadehra, MSc, MBA, VP, Operations, *(by phone)*

(b) (4)
(b) (4) Consultant to Polarean
(b) (4) Consultant to Polarean
(b) (4) Consultant to Polarean, *(by phone)*

1.0 BACKGROUND

On December 17, 2015, Polarean, Inc (herewith referred to as the sponsor) submitted a meeting request to the Division of Medical Imaging Products to discuss the Phase 3 program for Xenon 129 drug/device combination product. Specifically, as stated in the sponsor's meeting package, the sponsor wants to address the following objectives:

- Obtain Agency agreement that adequate preliminary evidence is available supporting the efficacy and safety of hyperpolarized ¹²⁹Xe scans to detect and quantify ventilation defects in order for Polarean to progress to Phase 3 confirmatory trials;
- Obtain Agency feedback on the 2 proposed Phase 3 studies to evaluate patients with asthma and patients with COPD;
- Obtain Agency agreement on the proposed pediatric waiver for patients <6 years of age;
- Obtain Agency feedback on specific questions regarding the device portion of the hyperpolarized ¹²⁹Xe gas drug/device combination product to establish a clear pathway to approval.

A type B meeting was granted on January 6, 2016, to occur on March 3, 2016. Prior to this meeting, FDA had a type C meeting with Polarean on May 20, 2015, to discuss the development of the sponsor's drug/device combination product.

FDA sent Preliminary Comments to Polarean on March 2, 2016.

2. DISCUSSION

We have reviewed the Meeting Package submitted on January 29, 2016 and provide the following responses to your questions. Your questions are in italic and our responses are in bold font.

FDA Introductory Comments

We appreciate your efforts to develop an imaging test for identifying and quantifying ventilation defects using Xe-129 MRI. We reference the following statement from your meeting package: “Therefore, there is a real unmet medical need for a diagnostic procedure or test that provides physicians with a clear and definitive view of the extent and distribution of regional ventilation defects. A test that can directly visualize the presence of ventilation defects as well as quantify those defects would also be instrumental for patients with ventilation defects”. At this time, based on our understanding of the pathophysiology and assessment of patients with asthma and COPD and your proposed clinical use, we do not agree with this statement.

We note that the use of imaging studies for the diagnosis of asthma, COPD, or cystic fibrosis is not part of standard clinical practice. While there may be a role for this imaging information in clinical practice, the utility of this imaging for the purposes of detecting early ventilation defects in patients who may or may not have COPD or asthma is unclear. While imaging may be done in these patients, the primary reason would not be to make a diagnosis of these conditions.

Regarding COPD, it is well understood that the contribution of the small airways to airflow resistance is small (because of the large cross sectional area in this zone) therefore; early small airway changes of COPD may not be measured by PFTs (FEV1). However, patients with COPD who are asymptomatic will not require treatment. Furthermore, patients who are dyspneic because of COPD would already have lung function impairment that would be detected with spirometry. While the degree of lung function impairment (FEV1) does not correlate with dyspnea symptoms, patients with normal lung function (FEV1) are not usually dyspneic.

For asthma, a chronic respiratory disorder that waxes and wanes, the utility of imaging to confirm the diagnosis is also questionable. We note that in both symptomatic asthma and COPD, diagnoses would be made based on the totality of clinical presentation.

We recommend you reassess the proposed clinical utility of Xe-129 MRI in order to develop future clinical studies to assess the performance of the test in a defined clinical setting where clinical utility is either accepted or demonstrated in clinical studies.

Summary of General Discussion

Based on the preliminary comments received, the sponsor preferred having an interactive discussion regarding the clinical utility of their product rather than focusing on the individual responses to the submitted questions. Below is a summary of that discussion.

The sponsor believes their product, hyperpolarized xenon, has the same clinical utility as spirometry. They stated that neither spirometry nor hyperpolarized xenon can be used as a stand-alone test. According to the sponsor, hyperpolarized xenon can overcome some limitations of spirometry. A handout was provided showing where pulmonary function tests (PFTs) do not give enough information for certain patient groups and how the hyperpolarized xenon scan may be of benefit for this population. The sponsor mentioned several examples where PFTs may not be consistent with a patient's clinical presentation, such as: patients with cystic fibrosis who are symptomatic but have normal PFT; patients with COPD with increasing symptoms but no appreciable change in PFT; or patients who are clinically dyspneic but have normal PFTs.

FDA stated that the sponsor needs to better describe how the performance of the test will be demonstrated in patient groups in which PFT or other standard tests are negative or inconclusive. FDA provided examples of conditions in which the potential clinical utility of the test could be demonstrated using an active comparator. The examples include pre-operative evaluation of lung ventilation and perfusion prior to lung resection surgery, or evaluation of ventilation/perfusion in patients suspected of having pulmonary embolism. FDA emphasized to the sponsor that visualization of lung defects by Xe-129 MRI in symptomatic patients with normal PFT is not sufficient. Clinical utility has to be demonstrated by establishing the reproducibility and importance of any lung defects by evaluating clinical outcomes such as the development of objective evidence of new or worsening pulmonary dysfunction consistent with baseline Xe-129 MRI defect.

The sponsor mentioned that up to a third of patients with dyspnea may have normal PFTs and that clinicians could use hyperpolarized xenon 129 scans as an alternative test in these patients. FDA reiterated they don't view this as a valuable study population for determining the clinical utility of the test. FDA suggested that the sponsor revise their proposed clinical protocols and develop a more specific patient population to evaluate the performance of hyperpolarized xenon 129; for example a COPD population with emphysema with no symptoms and normal PFTs. FDA recommended the sponsor design clinical studies utilizing a truth standard or an acceptable imaging comparator. It was suggested the sponsor use the approved product, Xenon 133, as an active comparator and show some measure of agreement. Alternatively, the sponsor can also consider using Tc99m DTPA as a comparator, even though this product is not approved in the United States.

The sponsor asked if they could provide protocols for comment along with a draft indication statement. FDA agreed.

(b) (4)

(b) (4)

FDA mentioned that during the May 2015 meeting they had expressed concern about the need for microbial testing. FDA clarified that they re-examined the issue of microbial testing and agree with the sponsor that the risk of microbial contamination is low and further testing is not necessary.

Post-meeting comment:

(b) (4)

(b) (4)

Clinical and Statistical

Question 1 Does FDA agree that there is adequate preliminary evidence from the GE-141-001 study and from the literature ($n=103$ subjects exposed to 1 or more doses) supporting the efficacy and safety hyperpolarized ^{129}Xe scans to detect and quantify ventilation defects in order for Polarean to progress to Phase 3 confirmatory trials?

FDA Response to Question 1:

The exploratory data seems to support further development of Xe-129 for assisting in detecting ventilation defects. However, we encourage you to review our preliminary meeting responses sent to you on May 18, 2015, and the minutes of our meeting discussion that occurred on May 20, 2015, so that you may further refine your proposed clinical studies. As mentioned above, we strongly recommend you further develop the clinical utility of this test in the proposed patient populations.

Question 2 Does FDA agree with Polarean's proposed use of standard pulmonary tests as the truth standard for the detection and quantification of ventilation defects?

FDA Response to Question 2:

We agree that spirometry can identify the presence and severity of airflow obstruction. However, from a regulatory perspective we recommend you design your studies to compare the results of Xe-129 MRI to an acceptable imaging test (reference standard) as well as pulmonary function tests (comparator tests). We again refer you to our written

preliminary comments and the meeting minutes from our discussion on May 20, 2015, regarding this topic.

We note the following statement in your meeting package: “Under certain circumstances, measurements of lung volume are essential for a physician to make a physiological diagnosis. It is important to note that PFTs are known to be insensitive to detecting ventilation impairment in small airways, which is common in early asthma and chronic obstructive pulmonary disease (COPD) (Usmani et al., 2012)”. This statement seems to imply that Xe-129 MRI may offer improved performance over PFTs, likely necessitating the need for reference standard imaging test to measure the true performance of this imaging modality. It seems that visualizing (localizing) ventilation defects will be an important aspect of the clinical utility that Xe-129 offers in the proposed patient population. Thus, we recommend including localization of ventilation defects as part of your study endpoints and analyses.

Question 3

The proposed Phase 3 study is an open-label study designed to evaluate the detection and quantification of ventilation defects in patients with asthma. Does FDA have any comments regarding the adequacy of the study design, specifically:

- a) Patient population;*
- b) Sample size;*
- c) Efficacy assessments;*
- d) Safety assessments, or*
- e) Sample size estimation and statistical methods?*

FDA Response to Question 3:

Please see our introductory comments as we question the utility of this imaging agent as a diagnostic tool in asthma.

Question 4 *The proposed Phase 3 study is an open-label study designed to evaluate the detection and quantification of ventilation defects in patients with COPD. Does FDA have any comments regarding the adequacy of the study design, specifically:*

- a) Patient population;*
- b) Sample size;*
- c) Efficacy assessments;*
- d) Safety assessments, or*
- e) Sample size estimation and analytic methods?*

FDA Response to Question 4:

Please see our introductory comments and those regarding comparators and reference standards. We recommend you think critically about the specific clinical use in this patient population and revise your proposed study protocol.

Question 5 Assuming the proposed Phase 3 prospective studies (Section 9.1.3 [Appendix 2] and Section 9.1.4 [Appendix 3]) meet their primary efficacy objectives, does FDA agree that sufficient efficacy data would be available from the Phase 3 program, the GE-141-001 study, and the literature to support an NDA for the broad indication of the detection and quantification of ventilation defects and that no other efficacy studies would be required?

FDA Response to Question 5:

It is premature to comment at this time.

Question 6 Assuming that the proposed Phase 3 prospective studies (Section 9.1.3 [Appendix 2] and Section 9.1.4 [Appendix 3]) demonstrate adequate evidence of safety, does FDA agree that sufficient safety would be available from the Phase 3 program, the GE-141-001 study, and the literature to support an NDA for the broad indication of the detection and quantification of ventilation defects and that no other safety studies would be required?

FDA Response to Question 6:

The proposed safety database appears reasonable.

Pediatric Waiver

Question 7 Does FDA agree that a waiver for pediatric subjects <6 years of age is appropriate for hyperpolarized ¹²⁹Xe scans?

FDA Response to Question 7:

Your proposal to request a waiver for pediatric patients less than 6 years of age appears appropriate. Your request will be considered during the review of your iPSP (which should identify the criteria of the waiver for this group) and a final determination will be made during review of your NDA.

Question 8 Does FDA agree that a deferral for pediatric subjects ≥6 years of age is appropriate for hyperpolarized ¹²⁹Xe scans?

FDA Response to Question 8:

Your proposal to request deferral of studies in pediatric patients 6 years of age and older appears appropriate. Your request will be considered during the review of your iPSP and a final determination will be made during review of your NDA.

Question 9 Does FDA agree that conducting a study (b) (4) would be sufficient to satisfy the pediatric requirements for our novel drug-device combination product for the detection and quantification of ventilation defects?

FDA Response to Question 9:

Please refer to the introductory comment above. At this time it is unclear what patient population is most appropriate. Ultimately, the pediatric population selected for your product will need to be a population in which there is a clinical need to evaluate the enrolled pediatric patients for possible ventilation defects.

(b) (4)

Microbial Limits Testing

***Question 10** Does FDA agree, based on the procedures followed in standard gas manufacture, the potential for microbial contamination will be low, and no additional microbial testing of the gas blend is necessary?*

FDA Response to Question 10:

As the potential for microbial contamination will be low if cGMP procedures are followed during the manufacture of the gas blend, the Agency agrees that microbial testing of the gas blend is not necessary. Please provide your rationale for waiving microbiological testing in your NDA.

***Question 11** Does FDA agree, based on the procedures followed in preparation of the hyperpolarized ¹²⁹Xe and the environment of the hyperpolarizer, the risk of microbial contamination is low, and no additional microbial testing of the hyperpolarized gas is necessary?*

FDA Response to Question 11:

The Agency agrees that the risk of microbial contamination is low and microbial testing is not necessary if the procedures described for preparation of the hyperpolarized ¹²⁹Xe are followed. Please provide your rationale for waiving microbiological testing in your NDA.

Device

***Question 12** Does the FDA agree that manufacturer registration is the only required information for the:*

- a. Delivery bag?*
- b. Mouthpiece?*

FDA Response to Question 12:

No, FDA does not agree that the only information required for submission is the manufacturer registration. We are not aware of any Class I delivery bag and mouthpiece intended to be used with hyperpolarized 129Xe. Further, the delivery bag serves as a drug container closure in which it appears that the drug can be stored for several hours. At this point the entire system (delivery bag and mouthpiece along with the xenon and other device constituent parts) is investigational; and testing should be conducted to verify safety and performance. Please see the comments below for additional information to provide for the evaluation of the safe use of the bag and mouth piece device constituent parts.

Additional FDA comments about questions 12(a) and 12(b)

- 1. In your submission, you state,**

(b) (4)

However, you have not provided any testing to demonstrate this. Please provide complete test reports to characterize the delivery bag and mouthpiece to ensure compatibility with hyperpolarized 129Xe and patient safety. This testing may include but is not limited to testing to demonstrate that the delivery bag does not leak, adequate sealing between the delivery bag, tubing, and mouthpiece, and compatibility of the delivery bag and mouthpiece with hyperpolarized 129Xe.

- 2. You have not proposed any testing to demonstrate the biocompatibility of your device. Your device is a combination product which delivers hyperpolarized 129Xe and the safety of the device in combination with hyperpolarized 129Xe has not been evaluated and tested with your labeled patient population. Materials that are in contact with the patient's gas pathway (either direct or indirect) are classified as externally communicating with tissue contact. Please conduct appropriate biocompatibility testing on any parts of your device that may contact humidified or rebreathed air per FDA General Program Memorandum #G95-1, which can be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080742.htm>.**

Please also conduct extractable and leachables (E&L) testing using nitric oxide for 15 hours to reflect the use of the device constituents and to provide worst case exhaustive extraction condition for this test. As part of this testing, please provide a quantitative and qualitative estimate of all leachables and residues originating from the device components/accessories that will be contacting patient gas path. We recommend that you follow the FDA-recognized standard ISO 10993-12:2007 Biological evaluation of medical devices - Part 12: Sample preparation and reference Materials and use an exhaustive extraction method (e.g. 50 °C 72 hrs) and both polar and non-polar solvents for preparation of the test samples. A complete study report including a description of the sample preparation, analytical methods and instrumental limits used, and chromatograms to assess the residues would be necessary for evaluation.

Afterwards, please perform an inhalational risk assessment (exposure and safety assessment) for all residues identified, including the organic, inorganic, organometallics, metals, and other residues. Your assessment should include a risk characterization, margin of safety calculation, the body weight, the reference doses/LOAELs/NOAELs, the limit of detections (LODs), the limit of quantifications (LOQs), the exposure assessment, and etc. for each extractables and leachables observed from your E&L study. For analysis of the leachable and extractable residues and the allowable limits, you may refer to the published toxicological literature. In addition, please provide a clear rationale for the uncertainty values that are used in the safety assessment for each residue.

To ensure the safety of your device constituents in delivering nitric oxide gas, please also conduct testing for Particulate Matter (PM) and Volatile Organic Compounds (VOC) to show that your device does not produce air that has been adulterated by the addition of these particles/compounds.

Please include the specifications and compositions for any resins (Per 21 CFR 177) used in the manufacture of either the bag or mouthpiece, along with appropriate certificate(s) of analysis and/or reference(s) to drug master files.

Question 13 Does FDA agree with the classification (b) (4) of the risks as provided in the Risk Matrix in Table 6?

Question 15 Does FDA agree with the classification of the risks (b) (4) as provided in the Risk Matrix in Table 7?

FDA Response to Question 13 and 15:

No, we do not agree with the classification of the risks (b) (4) as provided in the briefing document. For Class III devices, which would be relevant to the evaluation of this combination product, FDA determines whether PMA applications provide a reasonable assurance of safety and effectiveness by weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use, among other relevant factors.

Good documentation of risk management decisions by manufacturers helps streamline the premarket review process, and based on the limited information in the briefing document, we cannot assess the acceptability of your risk management system. Your risk management decisions are directly and indirectly evaluated in your submission including those pertaining to risk estimation, risk evaluation, risk acceptability, risk control measures, and overall residual risk.

You state that (b) (4)

However, we cannot assess the acceptability of your risk management system as you only provided information about the identification of risks. Other important information related to the evaluation of your risk management system was not included. Such information would include, for example, the risk control methods, verification of the risk control measures, and an estimate of residual risk. In addition, if mitigations include operator training (such as for misinterpretation of data) proposed labeling should be included in the submission.

In your briefing document, you outline your risk analysis noting that the risk analysis was performed using FMEA principles. FMEA (failure mode and effects analysis) is one possible tool available to use as part of risk identification and development of risk control measures. Risk management or device hazard analysis should include more than risk identification. A complete hazard analysis should include:

- identification of the hazardous event
- severity of the hazard
- cause(s) of the hazard
- method of control (e.g., alarm, hardware design)
- corrective measures taken, including an explanation of the aspects of the device design/requirements, that eliminate, reduce, or warn of a hazardous event
- verification that the method of control was implemented correctly

In your risk analysis, you have included mitigations in the explanation of risk, which presents challenges to identifying the method of risk control and evaluating whether appropriate corrective measures and verification/validation steps have been taken. Please provide an updated hazard analysis or risk management document in tabular form that includes all identified hazards, estimates of severity and probability, cause(s) of the hazard, method of control, corrective measures or mitigations, and verification of the risk control measure, and a residual risk analysis.

You may consider using the FDA recognized consensus standard ISO 14971: Medical Devices – Applications of Risk Management to Medical Devices (FDA recognition numbers 5-40 and 5-70). Please clarify if your risk management system conforms to this standard. If not, please provide an overview of your risk management system. Other formats of risk management may be acceptable, provided that all the components of a comprehensive risk management document are addressed.

For medical electrical equipment, we strongly encourage conformance to the currently FDA-recognized standards related to basic safety and electromagnetic disturbances including ANSI/AAMI 60601-1 Medical electrical equipment: Part 1: General requirements for basic safety and essential performance and ANSI/AAMI 60601-1-2 Medical Electrical Equipment: Part 1-2: General requirements for basic safety and essential performance – Collateral Standard: Electromagnetic disturbances – Requirements and tests. Conformance to these standards provides assurance that appropriate risk controls measures are in place related to topics ranging from electrical hazards to mechanical hazards to construction of the equipment to electromagnetic

compatibility to fault conditions and more.

Please refer to the [Recognized Consensus Standards](#) database to obtain the current list of recognized consensus standards.

Comment specific on risk 18

Risk 18 – “Someone with a medical implant being exposed to a magnetic field”

You note that this risk is mitigated by warning labels on unit. However, you indicate that the magnet field is highly localized (b) (4)

(b) (4) **In general, hazard mitigation by design is preferable to risk control through labeling or signage. Please consider physical barriers built into the device in addition to labeling to prevent exposure of individuals with medical implants to the magnetic field. This may alleviate need for a dedicated room with controlled access to address this hazard. While a dedicated room and controlled access may be one possible method of risk control, numerous projectile events related to MR systems serve as a cautionary tale to the limitations of warning signs and a dedicated room.**

Question 14 Does FDA agree that no Human Factor testing is required for the identified risks for the Polarization Measurement Station?

Question 16 Does FDA agree that Human Factor testing is not required for the Hyperpolarizer?

FDA Response to Questions 14 and 16:

No, at this time, it is premature to make this assessment. You have provided FMEA severity and occurrence matrix identifying classification zones; however, it is not clear if there was any identification or analysis of critical tasks of use. The agency requests Human Factors (HF) evaluation and summative testing data for critical tasks of use, those tasks where a use error could lead to clinical harm. Note that it is often not possible to estimate the probability of occurrence for use errors and it is necessary to evaluate the risk on the basis of the nature of the harm alone. Please provide the information below in order to assess whether Summative Human Factors test data will be requested for your combination product.

The following Human Factors data form the basis of Summative Human Factors testing to support a conclusion that the device user interface supports safe and effective use. This same data will establish when no further summative human factors testing is necessary for submission.

- a) An overview of intended device users or user populations (e.g., prescribing clinicians, technicians, etc.) and considerations for any unique or compelling characteristics regarding knowledge, expectations, capabilities, training or experience that could limit their ability to interact with the device user interface (UI).**

- b) **Consideration of the device use environment and its potential to impact to the ability of users to use the device successfully (e.g., lighting, noise, etc.).**
- c) **An identification of the device UI, noting that the UI includes all points of interaction between the user and the device such as controls, displays, packaging, labeling, training, alarms, etc. For example, Users will have to interact with multiple device components (hyperpolarizer, gas bag and mouthpiece, and hyperpolarization measurement station) to produce the hyperpolarized ^{129}Xe , provide the bag to the patient, affix the mouthpiece to the bag, have the patient inhale the correct dose at the correct time and acquire the appropriate MR images.**
- d) **A summary of known use problems for predecessor or similar devices.**
- e) **An analysis of user tasks including assigning criticality to tasks for which inadvertent use error (including failure to perform the task) could or would cause clinical harm. Identified “critical tasks” should be the focus of subsequent simulated use testing. Note, it is often not possible to estimate the probability of occurrence for use errors, for the critical task performance, and it is necessary to evaluate the risk on the basis of the nature of the harm alone. Therefore, critical tasks that are performed infrequently should not be excluded from evaluation in HF testing and any task failures or difficulties found during testing should have a follow-up root cause analysis. For example, you note that users should confirm (measure and record) the ^{129}Xe polarization just prior to subject administration, within 5 minutes. You provide estimates**

(b) (4)

(b) (4)

(b) (4)

Therefore, use related errors, such as unnecessary delays or measurement errors or improper dose delivery could negatively impact MR signal strength and image quality.

For example, in your future submission, please describe typical clinical workflow beginning with use of the hyperpolarizer through MR scanning of the patient (similar to Figure 2 in section 10.4 of the Type C brief package). Please provide expected personnel, times, and locations of devices and personnel associated with each step. In this updated flow diagram, please include patient positioning in the MR scanner and any preliminary MR protocols (prior to hyperpolarized ^{129}Xe administration and imaging). Please comment on the expected time from hyperpolarization measurement to delivery, appropriate mitigations, and potential impact on imaging. If the safety or effectiveness could be negatively impacted by use error, human factor testing may be appropriate to mitigate these risks.

If based on this analysis, critical tasks are identified, please provide a summative HF validation study based on simulated use of critical tasks, representing actual use. This study should evaluate a representative sample of 15 participants from each distinct user group. Upon completion of simulated use scenarios then subjective investigation of task specific performance can take place. The HF validation study protocol should outline a plan for the recording of results including performance data and subjective data regarding critical tasks. Performance data identifies task failures, close calls or serious difficulties and subjective data is derived from interviews with test participants

following simulated device use, including each test participant's perspective on the use of the device overall, any difficulties or confusion they experienced, and any of the tasks for which failure, close call, or difficulty occurred. Findings from these two data sets can then be evaluated for potential use errors and root cause analysis. Note that root cause evaluation should include specific consideration and feedback from test participants involved with the findings.

In addition, please note, these device components are controlled via computer software to obtain polarization and polarization measurements. FDA expects software design and validation activities to incorporate user testing. In other words, FDA expects human factors engineering to be woven into the entire software (and hardware) design and development process, including the device design requirements, analyses, and tests. Documentation of this testing should be included in the software documentation provided in your submission.

Regulatory and Procedural

Question 17

(b) (4)

FDA Response to Question 17:

(b) (4)

Question 18 Does FDA agree that minor changes made to the hyperpolarizer or polarization measurement station device components that only require “documentation” per the flowcharts described would only be reported as annual reportable changes, specifically:

- a. Prior to initiating the Phase 3 studies?*
- b. While the Phase 3 studies are ongoing?*
- c. Post-approval?*

FDA Response to Question 18:

No, we do not agree. For premarket development changes, all changes made should be submitted in accordance with IND submission requirements along with any additional information consistent with 21 CFR 812.

Regarding post market changes, while FDA has not published final guidance, there are preliminary principles available in the draft guidance, Guidance for Industry and FDA Staff: Submissions for Postapproval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA. Also, please see FDA meeting responses of May 20, 2015, questions 20-22 that indicate this is a PMA level device constituent.

Additional FDA Comments

Question 19 What additional comments and advice does FDA have regarding the hyperpolarized ¹²⁹Xe gas program?

FDA Response to Question 19:

We acknowledge that you plan to reference a drug master file regarding production of ¹²⁹Xe. Include all details of the manufacturing and controls of (b) (4) ¹²⁹Xe.

Regarding your overall drug development program (these comments are not directed solely to your initial protocol)

- 1. Determine an optimal dose, optimal MR sequences, and optimal acquisition parameters, prior to performing large studies that will be the primary basis of efficacy and safety.**
- 2. Characterize the PK, elimination and dose proportionality of Xe-129 in humans. If you plan to extrapolate this information from radioactive Xe-133, the literature studies must be adequate and the methods and results summarized in detail.**
- 3. FDA expectations for the performance of the analytical methods used for blood drug concentration determination can be found in the May, 2001 Guidance *Bioanalytical Method Validation* located at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf>**

3.0 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 (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. 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 PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

4.0 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 (cdcr-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>

5.0 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>.

6.0 505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of

such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX "TRADENAME"</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY "TRADENAME"</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

7.0 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).

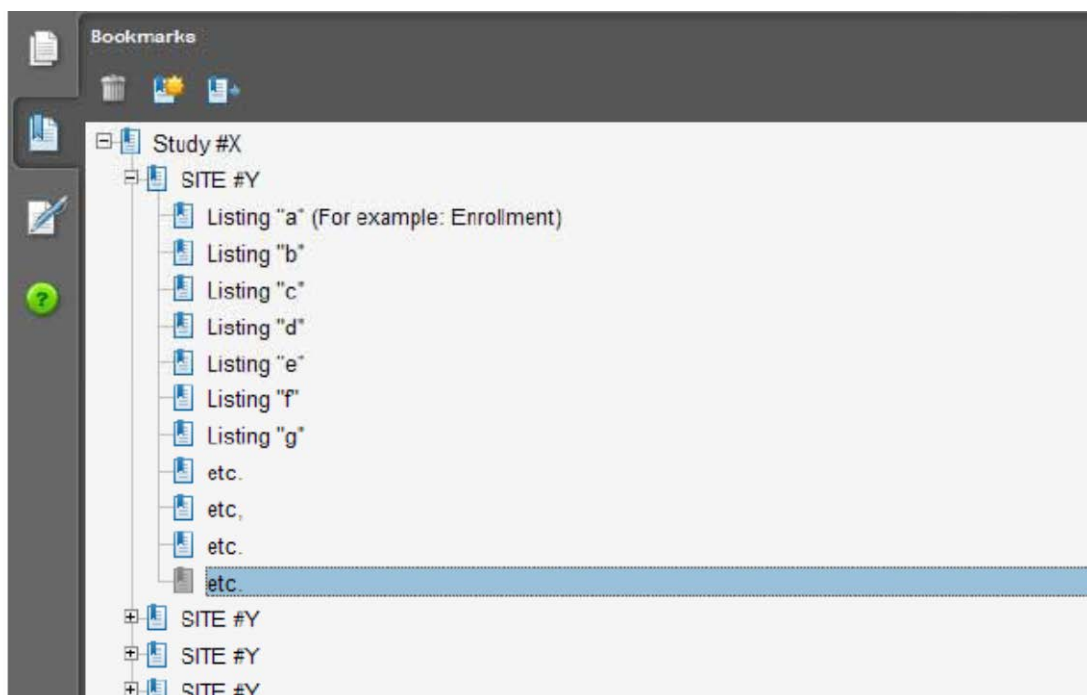
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

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.

8.0 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>.

9.0 NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

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.

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

10.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion

11.0 ACTION ITEMS

Sponsor will provide a draft protocol for FDA to review and comment

12.0 ATTACHMENTS AND HANDOUTS

Sponsor's Handout

1 Page has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

ALBERTA E DAVIS WARREN
03/31/2016