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RESEARCH**

APPLICATION NUMBER:

205098Orig1s000

OTHER REVIEW(S)

NDA 205098

Project Manager Overview
NDA 205098
Varithena (polidocanol injectable foam)

Background:

NDA 205098 was submitted pursuant to section 505(b)(1) of the FD&C act and was received by the Division of Cardiovascular and Renal Products (the Division) on February 4, 2013 and filed on April 5, 2013. The applicant seeks approval of polidocanol injectable foam for the indication of treatment of incompetent great saphenous veins, accessory saphenous veins and visible varicosities of the great saphenous vein (GSV) system above and below the knee and improvement of the symptoms of superficial venous incompetence and the appearance of visible varicosities in the GSV system. The application was given a Standard review and the PDUFA goal date set as December 4, 2013.

This NDA was the subject of investigations under IND 063420. The following milestone meetings were held with the applicant under that IND:

- End of Phase 2 (June 29, 2009)
- Pre-NDA (March 26, 2012 – CMC)
- Pre-NDA (December 14, 2012 – CMC, Written Response)
- Pre-NDA (July 31, 2012 – Clinical)

This application was reviewed by the Pediatric Review Committee (PeRC) on October 30, 2013 and granted a full waiver.

The overall compliance recommendation in EES is Acceptable as of November 22, 2013.

NDA Reviews and Memos

Division Director's Memo

Dr. Norman Stockbridge; November 25, 2013

In his memo Dr. Stockbridge summarizes that the remaining issues barring approval have been resolved and conveys the Division's decision to approve the application.

CDTL Memo

Dr. Khin U; November 14, 2013

Recommended Action: Approvable

In his memo, Dr. U stated that his recommendation is to approve the application, pending a satisfactory facilities inspection, resolution of outstanding information requests, and finalization of a review from DRISK.

Clinical Review

Dr. Khin U; July 12, 2013

Recommended Action: Approvable

In his review, Dr. U summarizes that the application is approvable from a clinical perspective.

Statistical Review

Dr. Steven Bai; July 2, 2013

In his review, Dr. Bai summarizes that the efficacy of the pooled PEM was consistently demonstrated across efficacy endpoints and both studies presented.

Clinical Pharmacology

Dr. Peter Hinderling; October 30, 2013

Recommended Action: Approvable

Please see review for details.

Pharmacology Review

Dr. William Link; September 5, 2013

Recommended action: Approvable

Please see review for details.

Chemistry Reviews

Dr. Wendy Wilson-Lee; August 30, 2013; November 7, 2013; November 25, 2013 (CMC)

Dr. Banu Zolnik; March 18, 2013 (BioPharm)

Dr. Quynh Nguyen; April 24, 2013; October 17, 2013; November 14, 2013 (CDRH HF)

Dr. Martin McDermott; July 26, 2013 (CDRH Materials Scientist)

Ms. Jhumur Banik; August 8, 2013 (CDRH Bioengineering)

Dr. Stephen Langille; September 12, 2013 (Microbiology)

Recommended Action: Approval

In her final review of November 25, 2013, Dr. Wilson-Lee recommends the application for approval.

Consult/Other Reviews:

DMEPA

2013-06-18 – Trade Name Review

2013-10-01 – Usability Study Review

DRISK

2013-11-22 – REMS Review

OPDP

2013-10-31 – Labeling Review

2013-11-21 – Labeling Review

OSI

2013-06-28 – Clinical Inspection Summary

SEALD

2013-06-07 – PRO Evaluation

2013-11-22 – Labeling Review

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/s/

MICHAEL V MONTELEONE
11/25/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title¹	Varithena™ (polidocanol injectable foam) for Injection, for intravenous use
Applicant	Biocompatibles Inc.
Application/Supplement Number	NDA 205098
Type of Application	Original
Indication(s)	treatment of incompetent great saphenous veins, accessory saphenous veins and visible varicosities of the great saphenous vein system above and below the knee
Office/Division	ODE I/DCRP
Division Project Manager	Mike Monteleone
Date FDA Received Application	February 4, 2013
Goal Date	December 4, 2013
Date PI Received by SEALD	November 21, 2013
SEALD Review Date	November 22, 2013
SEALD Labeling Reviewer	Elizabeth Donohoe
Acting SEALD Division Director	Sandra Kweder

¹ Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item (**deficiency**).
- **YES:** The PI meets the requirement for this item (**not a deficiency**).
- **N/A:** This item does not apply to the specific PI under review (**not applicable**).

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Selected Requirements of Prescribing Information

Comment: The reference in Drug Interactions is incorrect; it currently references (5) and should reference (7).

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment: The drug name currently is in title case and should be in upper case: VARITHENA

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the 4-digit year.

Comment:

Selected Requirements of Prescribing Information

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.
Comment:
- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.
Comment:
- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.
Comment:
- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).
Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.
Comment:
- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.
Comment:
- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).
Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.
Comment:

Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Selected Requirements of Prescribing Information

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- NO** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: *The manufacturer's toll-free phone number is missing.*

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Selected Requirements of Prescribing Information

Comment: *In FPI Contraindications, a cross-reference made to W&P is incomplete; it should read: [see Warnings and Precautions (5.1)]. Also, in FPI D&A, Patient Counseling Information is cross-referenced; this should be removed as prescribers should only be directed to sections with more detailed information.*

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment: *This statement has been modified but, if agreed to by the review division, is acceptable.*

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Selected Requirements of Prescribing Information

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- N/A** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

ELIZABETH A DONOHOE
11/22/2013

ERIC R BRODSKY
11/22/2013

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, Acting SEALD Director.

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: November 21, 2013

To: Mike Monteleone
Regulatory Project Manager
Division of Cardiovascular and Renal Products(DCRP)

From: Emily Baker, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 205098**
OPDP Labeling Comments for Varithena (polidocanol injectable foam)

OPDP has reviewed the proposed Package Insert (PI) submitted for consult on October 29, 2013, for Varithena (polidocanol injectable foam). Our comments on the PI are based on the proposed labeling emailed to us on November 15, 2013. OPDP's comments are provided directly on the attached marked-up copy of the proposed PI.

Thank you for the opportunity to comment on the proposed material.

If you have any questions, please contact Emily Baker at 301.796.7524 or Emily.Baker@fda.hhs.gov.

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

EMILY K BAKER
11/21/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: November 14, 2013

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID

THROUGH: Ron Kaye, MA, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID

TO: Mike Monteleone, Project Manager, CDER/OND/ODEI/DCRP
Khin M U, Medical Officer, CDER/OND/ODEI/DCRP

SUBJECT: NDA 205098
Applicant: BTG International
Device Constituent: VARISOLVE Microfoam Delivery System
(Canister, Transfer Unit, Syringe)
Intended Treatment: Severe Varicose Veins
CTS: ICC 1300068/CON 133929

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ron Kaye, Human Factors and Device Use-Safety Team Leader

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CDRH Human Factors Review

Combination Product Device Information

Submission Number: IND 63420

Applicant: BTG International

Drug Constituent: Varisolve Polidocanol Endovenous Microfoam (PEM)

Device Constituent: Canister Delivery System

Intended treatment: treatment of severe varicose veins

CDRH Human Factors Involvement History

- 23-Jan-2012: CDRH HF was first requested to provide a review on the Human Factors protocol contained in the IND
- 5-Mar-2012: CDRH HF provided one comment on assessing the interaction between the physicians and their clinical staff
- 23-April-2013: CDRH HF provided consultative review on the human factors validation study report and identified one major deficiency
- 17-Oct-2013: CDRH HF provided consultative review on the Applicant's response to HF deficiency and identified one deficiency
- 14-Nov-2013: CDRH HF provided consultative review on the Applicant's response to HF deficiency and found the response acceptable.

Overview and Recommendation

The Division of Cardiovascular and Renal Products requested a consultative review from CDRH Human Factors team on the Applicant's response to human factors deficiency that was previously identified via the review of the human factors study report (SP2277) for the Polidocanol Endovenous Microfoam (PEM) Drug Delivery device. This device consists of two canisters, (b) (4) and a microfoam transfer unit to facilitate the filling of the syringe. CDRH HF team was previously consulted to review the HF study protocol, where CDRH provided a comment on providing better characterization of the user tasks that will be performed by the physicians and their clinical staff, and assessing the interaction between the two user groups. CDRH HF team was also consulted to review design risk analysis report and Human Factors/usability validation study report, where CDRH requested the Applicant's analysis of the use errors, close calls, and operational difficulties seen in the study in the context of whether they were caused by aspects of device design, or its labeling. CDRH also requested that the report should provide a conclusion with respect whether the device can be used safely and effectively. In the current submission, the Applicant provided an additional report including detailed discussion and implication of use errors, close calls, and difficulties seen as well as a conclusion with respect to safety and effectiveness.

Based on the additional analysis that the Applicant provided in the current submission, this consultant does not have any outstanding concerns regarding the study results and their implication on device design and IFU. However, upon further discussion with CDER reviewers, the Applicant has submitted additional changes to the IFU subsequent to the study. This consultant is unable to determine whether these changes improve use performance and do not

introduce new use-related problems. This consultant recommended that an information request (IR) be issued to the Applicant to provide detailed analysis on the additional changes.

The IR response indicated that the Applicant has analyzed the impact of the changes to the IFU and concluded that none of the changes would result in a use-related hazard that would adversely impact patient safety or efficacy. The Applicant provided a table that outlines all of the changes that have been made. Most of the changes were made to allow better flow of the document, to achieve better alignment between the IFU and the information contained in the NDA, to provide explicit language for specific instructional statements, and to comply with IFU content requirement. There were three changes that did not fit in the above categories, and the Applicant has provided a detailed analysis of possible use errors, and associated risks, which were categorized as not significant. This reviewer has found the Applicant's response acceptable, and has no further questions.

Appendix 1: Previous CDRH Human Factors IR Response Review (10/17/2013)

The Division of Cardiovascular and Renal Products requested a consultative review from CDRH Human Factors team on the response from the Applicant. CDRH HF requested that the Applicant provide a complete analysis of the study results by providing information the clinical consequences of the observed use errors/close calls/operational difficulties, and determining whether these results were caused by any aspects of the product design, labeling, and/or training, and whether modifications are required. Also, the Applicant was asked to provide their conclusion based on the study report results.

In the response, the Applicant stated that a complete report was inadvertently omitted from the Appendix in the Risk Management Plan.

The complete report provided additional discussion and analysis regarding the use errors that were seen in the study. Specifically,

- One participant did not correctly initiate the gas transfer. This participant did not twist the oxygen canister in the correct direction resulting in the canister being stuck to the polidocanol canister, and the participant was unable to move forward. After a new device was provided, the participant was able to attach the oxygen canister without any problem. the potential hazard is that the treatment would be postponed, and because the procedure is not medically life intervening procedure, there is no clinical consequence. This same participant did not wait for one minute prior to removing the oxygen canister. When asked about this error, the participant indicated that they forgot which step they were performing. This error would result in the system not producing microfoam and would have been unstable. In such a case, the user would open a new canister and proceed with the procedure. There is no clinical significance associated with this error.
- Two participants unable to remove the oxygen canister from the polidocanol canister. Both participants indicated that they would ask for help in actual use. The Applicant affirmed that there is no clinical impact for this use error.
- Three participants did not write the first use date on the canister. The participants were not sure if this had to be done after completing the task or by certain point in the process. The Applicant believes that no further mitigations would be necessary because both the IFU and training emphasize the need to record the first use and the canister has a labeled section to record the first use. In addition, the Applicant affirmed that there is no clinical impact for this use error.
- Two participants did not inspect for visible bubbles. The Applicant indicated that there are multiple checks that are in place for inspecting bubbles. The first is the staff assistant inspecting the syringe, and the second is the physician inspecting the manometer tubing. These checks are discussed in the IFU. The Applicant affirmed that the clinical significance is legible, and the clinical review team concurred with this.

Regarding the reported difficulties,

- Five participants had some operational difficulties in removing the oxygen canister but they were able to eventually remove the canister. As previously discussed, there is no clinical significance for the report difficulties.

- Eight participants had some operational difficulties in attaching the Microfoam Transfer Unit, and took a little longer to complete the task. No significant issue was identified.
- Five participants had some operational difficulty with aligning the Microfoam Transfer Unit with the Polidocanol track and took a little longer to complete the task. No significant issue was identified.

Based on the additional analysis that the Applicant provided in the current submission, this consultant does not have any outstanding concerns regarding the study results and their implication on device design and IFU. However, upon further discussion with CDER reviewers, the Applicant has submitted additional changes to the IFU subsequent to the study. This consultant is unable to determine whether these changes improve use performance and do not introduce new use-related problems. The following information request should be sent to the Applicant:

You submitted additional changes to the IFU subsequent to the human factors validation study. We are unable to determine whether these changes improve use performance and that they do not introduce new use-related problems. Please provide an analysis of the hazards associated with the aspects of the IFU that have been modified and the potential clinical consequences if users make errors while performing any tasks that involve the modified instructions. The analysis should also identify the mitigations strategies to control all serious use-related hazards and the methods to validate the effectiveness of those mitigations. Please note that additional questions may arise based on your response.

Appendix 1: Previous CDRH Human Factors Report Review (4/23/2013)

The Division of Cardiovascular and Renal Products requested a consultative review from CDRH Human Factors team on the Human Factors (HF) study report (SP2277) for the Polidoncanol Endovenous Microfoam (PEM) Drug Delivery device. This device consists of two canisters, (b) (4) and a microfoam transfer unit to facilitate the filling of the syringe. CDRH HF team was previously consulted to review the HF study protocol, where CDRH provided a comment on providing better characterization of the user tasks that will be performed by the physicians and their clinical staff, and assessing the interaction between the two user groups. The current submission includes a design risk analysis report and the Human Factors/usability validation study report.

The study was conducted with 45 participants across three user groups (15 physicians, 15 clinical staff, and 15 staff assistants). The clinical staff and staff assistants were only responsible for preparing, setting-up the device, and inspecting the microfoam in the syringe. The physicians were responsible for preparation, inspecting, injecting into a manometer tubing within 75 seconds from the microfoam generation, and performing a final inspection of the microfoam through the manometer tubing. Training was provided to all test participants with a minimum of four hours training decay. There were a total of nine use errors, five close calls, 23 operational difficulties where three of the operational difficulties resulted in use errors with moderator intervention.

A total of nine use errors were committed by seven participants:

- One participant did not correctly initiate the gas transfer by twisting the wrong direction (counter-clockwise versus clockwise). As a result, the oxygen canister became stuck and the moderator had to provide the test participant a new device. The participant was then able to correct and initiate the gas transfer process. This same participant did not wait for one minute prior to removing the oxygen canister. The moderator intervened and asked the participant to refer to the Quick Reference Guide, and the participant realized the one minute wait time.
- Two participants were unable to remove the oxygen canister without the moderator intervention. One of the two participants was unable to accomplish the task due to physical limitations. The other participant tried to disengage the canister but stopped because it was in a locking position.
- Three participants did not write the first use date. One indicated that the task is not part of their normal tasks that they would perform, and would delegate it to their clinical staff. Two indicated that they forgot.
- Two participants did not inspect for presence of visible bubbles in the syringe. Both prepared additional syringe and created acceptable microfoam.

A total of five close calls were observed in the study:

- One participant initially placed the canisters on the counter top with the oxygen canister on the bottom instead of the top. The participant saw the arrows on the oxygen canister and realized that they had an incorrect orientation. The error was corrected during your gas transfer.
- Four participants committed close calls during the flushing step with the syringe, however, they realized and discarded the syringe, and used a new syringe with a new microfoam.

A total of 23 operational difficulties were observed in the study:

- Two participants experienced difficulties with initiating gas transfer task – one showed some difficulty but was able to complete the task; one could not move the oxygen canister into the locked position due to diminished hand strength.
- Five participants experienced difficulty regarding the force required to remove the oxygen canister but were able to complete the task.
- Eight participants had difficulty with aligning the MTU with the Polidocanol track but were able to complete the task. Another five participants had difficulty with the same task when setting up for a new patient.

Review of this material identified one deficiency that should be transmitted to the Applicant:

We note that you included the design risk analysis and the Human Factors/usability validation study report in the Risk Management Plan section of your submission. Your HF/usability validation study showed that there were a total of nine use errors, five close calls, 23 operational difficulties where three of the operational difficulties resulted in use errors with moderator intervention. Your analyses of study results and of use-related risks did not clearly describe the potential negative clinical consequences of the observed use errors/close calls/operational difficulties. In addition, we expect that the test results, and particularly failures or patterns of subjective reports of difficulty with the use of the device should be discussed with respect to whether they were caused by aspects of the design of the device, its labeling, the content or proximity of training, and whether modifications are required. Furthermore, your study conclusion stated that the “interpretation of whether this device is safe and effective to use must be made by BTG since they possess the clinical understanding of the impact of these use errors.” We expect that the conclusion should clearly state whether device is reasonably safe and effective for the intended users, uses, and use conditions. Please provide us the information the clinical consequences of the observed use errors/close calls/operational difficulties, and whether these results were caused by any aspects of the product design, labeling, and/or training, and whether modifications are required. Also, please provide your conclusion based on the study report results.

Appendix 3: Previous CDRH Human Factors Protocol Review (3/15/2013)

Overview

The Division of New Drug Quality Assessment requested a Human Factors consultative review of the IND 63420 submitted by BTG International. In the cover letter dated 20-Feb-2012, the Applicant requests for comments and advice on the usability protocol and instructions for use before the pre-NDA meeting with the Agency scheduled on 26-Mar-2012. The VARISOLVE Polidocanol Endovenous Microfoam Delivery System is intended to treat patients with Severe Varicose Veins. This review provides CDRH's review and recommendations on the Human Factors related information contained in the IND. Please see the recommendation section for questions to be transmitted to BTG International.

Review Materials

Type B pre-NDA Meeting Request Package (dated 24-Feb-2012)

Usability Test Protocol PEM Delivery System (Draft, version 1.3, dated 8-Feb-2012)

Review of Human Factors Related Information

Summary of Human Factors/Usability Test Protocol

The product is shipped to the user in the form of a two-canister system. One canister contains the Polidocanol solution and carbon dioxide gas, and the other canister contains oxygen. When the contents of the two canisters are connected and activated the pressures equalize. These canisters have a connector unit, which keeps them separated during shipment and allows for easy transfer of the oxygen into the Polidocanol canister prior to use.

Description of User Interaction

Once the oxygen transfer into the Polidocanol canister is initiated, the user waits one minute then separates the canisters. A Microfoam Transfer Unit (MTU) is then mounted on the Polidocanol canister to complete the PEM delivery system. (b) (4)

When generating the microfoam, the user must prime and flush visible bubbles from the MTU and the syringe in order to produce a syringe full of usable microfoam. The microfoam is dispensed from the MTU into (b) (4) syringes, which are then utilized in the EMA procedure.

Once microfoam is created, the physician must inject it into the greater saphenous vein (GSV) or other selected vein via a manometer tube - placed earlier in the procedure - within 75 seconds of creation. If any visible bubbles are seen in the manometer tube, the physician should stop the injection, aspirate the visible bubbles back into the syringe, and discard its contents.

The PEM Polidocanol canister is a multi-access product, able to produce 3 (three) 5mL doses of microfoam per treatment. A total of 3 treatments can be done from one canister. A new MTU must be used for each patient/treatment.

Intended Users

The intended users for this product can be broken down into two user groups: physicians and clinical staff that provide treatment for varicose veins. The clinical staff includes a scrub nurse, a circulating nurse, and a duplex untra-sonographer. BTG International plans to recruit 20 physicians and 20 clinical staff for the study.

Device Use Environment

The typical use environment for the proposed product includes physician's office suite and/or hospital setting. The simulated use environment will represent realistic use environment.

Previous Human Factors Evaluations

BTG International have conducted several exploratory evaluations to develop and refine the Instructions for Use, and to implement measures to improve device design.

User Task Selection

Based on use-related risk analysis, and exploratory evaluations, the follow tasks have been determined to have critical influence on the safe and effective use of this device:

- Gassing of Polidocanol canister (oxygen transfer into Polidocanol canister)
- Attachment of MTU
- Generation of microfoam
- Inspection of Microfoam
- Changing of MTU

Data Collection and Analysis

Subjective and performance data will be collected during the study. Subjective data will include study participants feedback on use errors, close calls, and general difficulties. Performance data will focus on the defined critical use tasks including gas transfer time, hold time after transfer, microfoam use time, and visual inspection for visible bubbles.

Training

Upon product commercialization, training on the entire clinical procedure including product preparation, unique clinical procedures and interventions, and patient post-procedure activities will be provided to physicians and their staff. For the simulated use study, participant training will be limited to the information required to interact with the delivery system. Training on in vivo procedures will not be included. A product demonstration and a walk-through of the training materials including IFU will be provided to test participants. In addition, test participants will be asked to perform the gas transfer, attach the MTU, generate microfoam, inspect the microfoam for visible bubbles, and inject mircofoam into the manometer tubing while inspecting for visible bubbles. There will be a minimum of a 4 hours delay before testing will be introduced.

Review Recommendations

Overall, the proposed protocol appears adequate in terms of study methodology for:

- Defining the intended user population and extent of training necessary for the use of the product,

- Identifying simulated use environment that represents realistic use environment,
- Prioritizing and identify critical tasks based on risk assessment, and
- Collecting and analyzing the necessary data to demonstrate safe and effective use.

This protocol presents an interesting use scenario for which both the physicians and their clinical staff will be participating in the simulated use study. Based on the information presented in the study, it is unclear if physicians and clinical staff will have similar tasks or have specific and different task sets. It is also not clear whether or not the interaction between physicians and their clinical staff is critical in safe and effective use. In addition, a use-related risk analysis was not provided along with the Human Factors/usability validation study protocol. The Applicant should be asked to provide this analysis along with the rationale for the task selection for the study.

Please transmit the following comments to BTG International:

This protocol presents an interesting use interaction for which both the physicians and their clinical staff will be participating in the simulated use study as two separate user groups. However, when you referred to the “user” in the protocol, it is unclear if you refer to either the physicians and/or clinical staff. Please clarify whether physicians and clinical staff will perform similar tasks or have specific yet different task sets. Please provide a task and function analysis for the two intended user groups. Please also clarify whether the interaction between physicians and their clinical staff while using the device is critical in safe and effective use.

In addition, a use-related risk analysis was not provided along with the Human Factors/usability validation study protocol. Please provide this analysis along with the rationale for the task selection and inclusion in the study.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

Appendix 4: Device Description

The Polidocanol Endovenous Microfoam (PEM) system is used to create microfoam to treat an incompetent greater saphenous vein (GSV). The endovenous microfoam ablation (EMA) procedure is performed under duplex ultrasound, guidance and involves the injection of microfoam formulated from Polidocanol solution. The Varisolve PEM drug/device combination product is provided as two canister system: one of the cans contains polidocanol held under a carbon dioxide atmosphere and the other can contains pressurized oxygen. The Varisolve PEM microfoam is generated via a pressurized canister, and transferred to a syringe through the Microfoam Transfer Unit (MTU) for delivery into the vein. The polidocanol active pharmaceutical ingredient (API), canister, and transfer system are all part of proprietary drug generation system.



Figure 1: Varisolve System (after Activation with Oxygen)

Table 1: Polidocanol injectable microfoam Operation Steps

(b) (4)



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/s/

MICHAEL V MONTELEONE
11/18/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: October 17, 2013

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID

THROUGH: Ron Kaye, MA, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID

TO: Mike Monteleone, Project Manager, CDER/OND/ODEI/DCRP
Khin M U, Medical Officer, CDER/OND/ODEI/DCRP

SUBJECT: NDA 205098
Applicant: BTG International
Device Constituent: VARISOLVE Microfoam Delivery System
(Canister, Transfer Unit, Syringe)
Intended Treatment: Severe Varicose Veins
CTS: ICC 1300068/CON 133929

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ron Kaye, Human Factors and Device Use-Safety Team Leader

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CDRH Human Factors Review

Combination Product Device Information

Submission Number: IND 63420

Applicant: BTG International

Drug Constituent: Varisolve Polidocanol Endovenous Microfoam (PEM)

Device Constituent: Canister Delivery System

Intended treatment: treatment of severe varicose veins

CDRH Human Factors Involvement History

- 23-Jan-2012: CDRH HF was first requested to provide a review on the Human Factors protocol contained in the IND
- 5-Mar-2012: CDRH HF provided one comment on assessing the interaction between the physicians and their clinical staff
- 23-April-2013: CDRH HF provided consultative review on the human factors validation study report and identified one major deficiency
- 17-Oct-2013: CDRH HF provided consultative review on the Applicant's response to HF deficiency

Overview and Recommendation

The Division of Cardiovascular and Renal Products requested a consultative review from CDRH Human Factors team on the Applicant's response to human factors deficiency that was previously identified via the review of the human factors study report (SP2277) for the Polidocanol Endovenous Microfoam (PEM) Drug Delivery device. This device consists of two canisters, (b) (4), and a microfoam transfer unit to facilitate the filling of the syringe. CDRH HF team was previously consulted to review the HF study protocol, where CDRH provided a comment on providing better characterization of the user tasks that will be performed by the physicians and their clinical staff, and assessing the interaction between the two user groups. CDRH HF team was also consulted to review design risk analysis report and Human Factors/usability validation study report, where CDRH requested the Applicant's analysis of the use errors, close calls, and operational difficulties seen in the study in the context of whether they were caused by aspects of device design, or its labeling. CDRH also requested that the report should provide a conclusion with respect whether the device can be used safely and effectively. In the current submission, the Applicant provided an additional report including detailed discussion and implication of use errors, close calls, and difficulties seen as well as a conclusion with respect to safety and effectiveness.

Based on the additional analysis that the Applicant provided in the current submission, this consultant does not have any outstanding concerns regarding the study results and their implication on device design and IFU. However, upon further discussion with CDER reviewers, the Applicant has submitted additional changes to the IFU subsequent to the study. This consultant is unable to determine whether these changes improve use performance and do not introduce new use-related problems. This consultant recommends that the following letter ready request be sent to the Applicant:

You submitted additional changes to the IFU subsequent to the human factors validation study. We are unable to determine whether these changes improve use performance and that they do not introduce new use-related problems. Please provide an analysis of the hazards associated with the aspects of the IFU that have been modified and the potential clinical consequences if users make errors while performing any tasks that involve the modified instructions. The analysis should also identify the mitigations strategies to control all serious use-related hazards and the methods to validate the effectiveness of those mitigations. Please note that additional questions may arise based on your response.

Human Factors Review

The Applicant stated that a complete report was inadvertently omitted from the Appendix in the Risk Management Plan.

The complete report provided additional discussion and analysis regarding the use errors that were seen in the study. Specifically,

- One participant did not correctly initiate the gas transfer. This participant did not twist the oxygen canister in the correct direction resulting in the canister being stuck to the polidocanol canister, and the participant was unable to move forward. After a new device was provided, the participant was able to attach the oxygen canister without any problem. the potential hazard is that the treatment would be postponed, and because the procedure is not medically life intervening procedure, there is no clinical consequence. This same participant did not wait for one minute prior to removing the oxygen canister. When asked about this error, the participant indicated that they forgot which step they were performing. This error would result in the system not producing microfoam and would have been unstable. In such a case, the user would open a new canister and proceed with the procedure. There is no clinical significance associated with this error.
- Two participants unable to remove the oxygen canister from the polidocanol canister. Both participants indicated that they would ask for help in actual use. The Applicant affirmed that there is no clinical impact for this use error.
- Three participants did not write the first use date on the canister. The participants were not sure if this had to be done after completing the task or by certain point in the process. The Applicant believes that no further mitigations would be necessary because both the IFU and training emphasize the need to record the first use and the canister has a labeled section to record the first use. In addition, the Applicant affirmed that there is no clinical impact for this use error.
- Two participants did not inspect for visible bubbles. The Applicant indicated that there are multiple checks that are in place for inspecting bubbles. The first is the staff assistant inspecting the syringe, and the second is the physician inspecting the manometer tubing. These checks are discussed in the IFU. The Applicant affirmed that the clinical significance is legible, and the clinical review team concurred with this.

Regarding the reported difficulties,

- Five participants had some operational difficulties in removing the oxygen canister but they were able to eventually remove the canister. As previously discussed, there is no clinical significance for the report difficulties.
- Eight participants had some operational difficulties in attaching the Microfoam Transfer Unit, and took a little longer to complete the task. No significant issue was identified.
- Five participants had some operational difficulty with aligning the Microfoam Transfer Unit with the Polidocanol track and took a little longer to complete the task. No significant issue was identified.

Appendix 1: Previous CDRH Human Factors Report Review (4/23/2013)

DATE: April 23, 2013
FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID
THROUGH: Ron Kaye, MA, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID
TO: Mike Monteleone, Project Manager, CDER/OND/ODEI/DCRP
SUBJECT: NDA 205098
Applicant: BTG International
Device Constituent: VARISOLVE Microfoam Delivery System
(Canister, Transfer Unit, Syringe)
Intended Treatment: Severe Varicose Veins

Overview and Recommendation

The Division of Cardiovascular and Renal Products requested a consultative review from CDRH Human Factors team on the Human Factors (HF) study report (SP2277) for the Polidoncanol Endovenous Microfoam (PEM) Drug Delivery device. This device consists of two canisters, (b) (4) and a microfoam transfer unit to facilitate the filling of the syringe. CDRH HF team was previously consulted to review the HF study protocol, where CDRH provided a comment on providing better characterization of the user tasks that will be performed by the physicians and their clinical staff, and assessing the interaction between the two user groups. The current submission includes a design risk analysis report and the Human Factors/usability validation study report. Review of this material identified one deficiency that should be transmitted to the Sponsor:

We note that you included the design risk analysis and the Human Factors/usability validation study report in the Risk Management Plan section of your submission. Your HF/usability validation study showed that there were a total of nine use errors, five close calls, 23 operational difficulties where three of the operational difficulties resulted in use errors with moderator intervention. Your analyses of study results and of use-related risks did not clearly describe the potential negative clinical consequences of the observed use errors/close calls/operational difficulties. In addition, we expect that the test results, and particularly failures or patterns of subjective reports of difficulty with the use of the device should be discussed with respect to whether they were caused by aspects of the design of the device, its labeling, the content or proximity of training, and whether modifications are required. Furthermore, your study conclusion stated that the “interpretation of whether this device is safe and effective to use must be made by BTG since they possess the clinical understanding of the impact of these use errors.” We expect that the conclusion should clearly state whether device is reasonably safe and effective for the intended users, uses, and use conditions. Please provide us the information the clinical consequences of the observed use errors/close calls/operational difficulties, and whether these results were caused by any aspects of the product design, labeling, and/or training, and whether modifications are required. Also, please provide your conclusion based on the study report results.

Human Factors Review

The study was conducted with 45 participants across three user groups (15 physicians, 15 clinical staff, and 15 staff assistants). The clinical staff and staff assistants were only responsible for preparing, setting-up the device, and inspecting the microfoam in the syringe. The physicians were responsible for preparation, inspecting, injecting into a manometer tubing within 75 seconds from the microfoam generation, and performing a final inspection of the microfoam through the manometer tubing. Training was provided to all test participants with a minimum of four hours training decay. There were a total of nine use errors, five close calls, 23 operational difficulties where three of the operational difficulties resulted in use errors with moderator intervention.

A total of nine use errors were committed by seven participants:

- One participant did not correctly initiate the gas transfer by twisting the wrong direction (counter-clockwise versus clockwise). As a result, the oxygen canister became stuck and the moderator had to provide the test participant a new device. The participant was then able to correct and initiate the gas transfer process. This same participant did not wait for one minute prior to removing the oxygen canister. The moderator intervened and asked the participant to refer to the Quick Reference Guide, and the participant realized the one minute wait time.
- Two participants were unable to remove the oxygen canister without the moderator intervention. One of the two participants was unable to accomplish the task due to physical limitations. The other participant tried to disengage the canister but stopped because it was in a locking position.
- Three participants did not write the first use date. One indicated that the task is not part of their normal tasks that they would perform, and would delegate it to their clinical staff. Two indicated that they forgot.
- Two participants did not inspect for presence of visible bubbles in the syringe. Both prepared additional syringe and created acceptable microfoam.

A total of five close calls were observed in the study:

- One participant initially placed the canisters on the counter top with the oxygen canister on the bottom instead of the top. The participant saw the arrows on the oxygen canister and realized that they had an incorrect orientation. The error was corrected during your gas transfer.
- Four participants committed close calls during the flushing step with the syringe, however, they realized and discarded the syringe, and used a new syringe with a new microfoam.

A total of 23 operational difficulties were observed in the study:

- Two participants experienced difficulties with initiating gas transfer task – one showed some difficulty but was able to complete the task; one could not move the oxygen canister into the locked position due to diminished hand strength.
- Five participants experienced difficulty regarding the force required to remove the oxygen canister but were able to complete the task.
- Eight participants had difficulty with aligning the MTU with the Polidocanol track but were able to complete the task. Another five participants had difficulty with the same task when setting up for a new patient.

Appendix 2: Previous CDRH Human Factors Protocol Review (3/15/2013)

DATE: March 15, 2012
FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID
THROUGH: Ron Kaye, MA, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID
CC: Molly Story, PhD, Human Factors and Accessible Medical Technology Specialist, DAGID
TO: Wendy Wilson, PhD, Chemist, CDER/OPS/ONDQA/DNDQAI
Teshara Bouie, Project Manager, OPS/ONDQA/DNDQAI
SUBJECT: IND 63420,
Applicant: BTG International
Device Constituent: VARISOLVE Microfoam Delivery System
(Canister, Transfer Unit, Syringe)
Intended Treatment: Severe Varicose Veins

Overview

The Division of New Drug Quality Assessment requested a Human Factors consultative review of the IND 63420 submitted by BTG International. In the cover letter dated 20-Feb-2012, the Applicant requests for comments and advice on the usability protocol and instructions for use before the pre-NDA meeting with the Agency scheduled on 26-Mar-2012. The VARISOLVE Polidocanol Endovenous Microfoam Delivery System is intended to treat patients with Severe Varicose Veins. This review provides CDRH's review and recommendations on the Human Factors related information contained in the IND. Please see the recommendation section for questions to be transmitted to BTG International.

Review Materials

Type B pre-NDA Meeting Request Package (dated 24-Feb-2012)
Usability Test Protocol PEM Delivery System (Draft, version 1.3, dated 8-Feb-2012)

Review of Human Factors Related Information

Device Description

The Polidocanol Endovenous Microfoam (PEM) system is used to create microfoam to treat an incompetent greater saphenous vein (GSV). The endovenous microfoam ablation (EMA) procedure is performed under duplex ultrasound, guidance and involves the injection of microfoam formulated from Polidocanol solution.

The Varisolve PEM drug/device combination product is provided as two canister system: one of the cans contains polidocanol held under a carbon dioxide atmosphere and the other can contains pressurized oxygen. The Varisolve PEM microfoam is generated via a pressurized canister, and transferred to a syringe through the Microfoam Transfer Unit (MTU) for delivery into the vein. The polidocanol active pharmaceutical ingredient (API), canister, and transfer system are all part of proprietary drug generation system.



Figure 1: Varisolve System (after Activation with Oxygen)

Summary of Human Factors/Usability Test Protocol

The product is shipped to the uSer in the form of a two-canister system. One canister contains the Polidocanol solution and carbon dioxide gas, and the other canister contains oxygen. When the contents of the two canisters are connected and activated the pressures equalize. These canisters have a connector unit, which keeps them separated during shipment and allows for easy transfer of the oxygen into the Polidocanol canister prior to use.

Description of User Interaction

Once the oxygen transfer into the Polidocanol canister is initiated, the user waits one minute then separates the canisters. A Microfoam Transfer Unit (MTU) is then mounted on the Pondocanol canister to complete the PEM delivery system. (b) (4)

When generating the microfoam, the user must prime and flush visible bubbles from the MTU and the syringe in order to produce a syringe full of usable microfoam. The microfoam is dispensed from the MTU into (b) (4) syringes, which are then utilized in the EMA procedure.

Once microfoam is created, the physician must inject it into the greater saphenous vein (GSV) or other selected vein via a manometer tube - placed earlier in the procedure - within 75 seconds of creation. If any visible bubbles are seen in the manometer tube, the physician should stop the injection, aspirate the visible bubbles back into the syringe, and discard its contents.

The PEM Polidocanol canister is a multi-access product, able to produce 3 (three) 5mL doses of microfoam per treatment. A total of 3 treatments can be done from one canister. A new MTU must be used for each patient/treatment.

Intended Users

The intended users for this product can be broken down into two user groups: physicians and clinical staff that provide treatment for varicose veins. The clinical staff includes a scrub nurse, a circulating nurse, and a duplex ultra-sonographer. BTG International plans to recruit 20 physicians and 20 clinical staff for the study.

Device Use Environment

The typical use environment for the proposed product includes physician's office suite and/or hospital setting. The simulated use environment will represent realistic use environment.

Previous Human Factors Evaluations

BTG International have conducted several exploratory evaluations to develop and refine the Instructions for Use, and to implement measures to improve device design.

User Task Selection

Based on use-related risk analysis, and exploratory evaluations, the follow tasks have been determined to have critical influence on the safe and effective use of this device:

- Gassing of Polidocanol canister (oxygen transfer into Polidocanol canister)
- Attachment of MTU
- Generation of microfoam
- Inspection of Microfoam
- Changing of MTU

Data Collection and Analysis

Subjective and performance data will be collected during the study. Subjective data will include study participants feedback on use errors, close calls, and general difficulties. Performance data will focus on the defined critical use tasks including gas transfer time, hold time after transfer, microfoam use time, and visual inspection for visible bubbles.

Training

Upon product commercialization, training on the entire clinical procedure including product preparation, unique clinical procedures and interventions, and patient post-procedure activities will be provided to physicians and their staff. For the simulated use study, participant training will be limited to the information required to interact with the delivery system. Training on in vivo procedures will not be included. A product demonstration and a walk-through of the training materials including IFU will be provided to test participants. In addition, test participants will be asked to perform the gas transfer, attach the MTU, generate microfoam, inspect the microfoam for visible bubbles, and inject microfoam into the manometer tubing while inspecting for visible bubbles. There will be a minimum of a 4 hours delay before testing will be introduced.

Review Recommendations

Overall, the proposed protocol appears adequate in terms of study methodology for:

- Defining the intended user population and extent of training necessary for the use of the product,
- Identifying simulated use environment that represents realistic use environment,
- Prioritizing and identify critical tasks based on risk assessment, and

- Collecting and analyzing the necessary data to demonstrate safe and effective use.

This protocol presents an interesting use scenario for which both the physicians and their clinical staff will be participating in the simulated use study. Based on the information presented in the study, it is unclear if physicians and clinical staff will have similar tasks or have specific and different task sets. It is also not clear whether or not the interaction between physicians and their clinical staff is critical in safe and effective use. In addition, a use-related risk analysis was not provided along with the Human Factors/usability validation study protocol. The Applicant should be asked to provide this analysis along with the rationale for the task selection for the study.

Please transmit the following comments to BTG International:

This protocol presents an interesting use interaction for which both the physicians and their clinical staff will be participating in the simulated use study as two separate user groups. However, when you referred to the “user” in the protocol, it is unclear if you refer to either the physicians and/or clinical staff. Please clarify whether physicians and clinical staff will perform similar tasks or have specific yet different task sets. Please provide a task and function analysis for the two intended user groups. Please also clarify whether the interaction between physicians and their clinical staff while using the device is critical in safe and effective use.

In addition, a use-related risk analysis was not provided along with the Human Factors/usability validation study protocol. Please provide this analysis along with the rationale for the task selection and inclusion in the study.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

Appendix 3: Device Description

Table 1: Polidocanol injectable microfoam Operation Steps

(b) (4)



(b) (4)



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/s/

MICHAEL V MONTELEONE
10/23/2013

Martin (Ken) McDermott, Materials Scientist, 301-796-2621,
10903 New Hampshire Avenue
White Oak Building 64, Room 3072
Silver Spring, Maryland 20993-0002

DEPARTMENT OF HEALTH and HUMAN SERVICES
Food and Drug Administration
Center for Devices and Radiological Health
Office of Science and Engineering Laboratories
Division of Chemistry and Materials Sciences

Document # NDA 205098
Organiz CDER.
Product Name Polidocanol Injectable Microfoam, 1%
Firm/Sponsor Provensis Ltd.

CONSULT REQUEST

Review chemical interactions of the drug, gas and excipient with the device used to make the polidocanol injectable microfoam.

CONTENTS of this MEMO

1. Conclusions
2. Device description
3. How the device forms the microfoam
4. Materials in the device
5. Polidocanol solution contacting the device
6. Chemical interactions between polidocanol solution and the device
7. Additional information requested
8. Firm's response
9. Comments on the firm's response

CONCLUSIONS

Adequate responses to requests for additional information were received. The ingredients of the polidocanol injectable microfoam do not appear to be reactive to the materials of the device that stores and produces the foam as summarized below:

1. The O2 Canister is composed of aluminum with an (b) (4)
The canister holds O2 at 5.4 bar. The Aluminum and (b) (4)
were determined to be stable.
2. The Polidocanol Canister is composed of Aluminum. It holds the polidocanol solution for a maximum period of:
 - a. 18 months in carbon dioxide. The aluminum is stable in the pH range of the polidocanol solution.
 - b. 7 days in CO2-O2 gas mixture after the oxygen canister is attached. Corrosion was not demonstrated to occur within this time.

Aluminum content in the polidocanol solution had not changed at either 25°C or 40°C over a 3 month period (3.2.P.2). The method for measuring purity level was not discussed and the meaning of NMT (b) (4) was not defined. 4 Week aluminum levels do not change as a function of time (3.2.P.8.1).

3. Components of the device that generate and deliver the polidocanol foam are composed of (b) (4).

(b) (4) No degradation products were extracted nor was there a significant change in oligomer size of polidocanol. Surface chemical reactions could possibly alter the interaction between parts such as (b) (4). No change in the surface appearance of the (b) (4) suggest no changes in surface properties (3.2.P.2).

DEVICE DESCRIPTION

Polidocanol is a sclerosing agent and irritant, causing fibrosis inside varicose veins, occluding the lumen of the vessel, and reducing the appearance of the varicosity. The purpose of the device under review is to convert polidocanol solution into a sclerosing foam. Sclerosing foam is a mixture of gas bubbles in a liquid solution that contains surface-active molecules. The gas must be well tolerated by patients, physiologic, and the bubble size should be, preferably, under 100 µm.

A sclerosing foam increases the thrombogenic property of the drug 3.5 to 4 times over traditional liquid sclerotherapy because foam

1. displaces the blood allowing direct contact of the sclerosant with the endothelium, whereas liquid mixes with blood in the vein and dilutes the concentration of the sclerosant
2. requires a smaller total dose of sclerosant since liquid produces four or five times its volume in foam
3. is much better tolerated
4. is echogenic, which dramatically increases accuracy under ultrasound control
5. is not washed away as easily as the drug in the form of a solution.
6. can be directed into regions by manual manipulation via ultrasound-guided foam sclerotherapy.

HOW THE DEVICE FORMS THE MICROFOAM

The components and each step in the formation of the microfoam consists of the following:

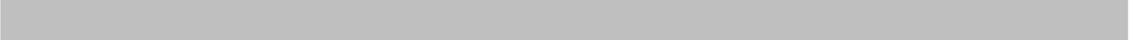
LIQUID

1. A “polidocanol canister” contains 18 mL of 1.0 % w/w polidocanol solution at 1.2 bar of carbon dioxide.
2. Activation means formation of the macrofoam, which is achieved when an “Oxygen Canister” (5.4 bar) is attached to and pressurizes the polidocanol canister
3. In the polidocanol canister, the oxygen and carbon dioxide gas mixture (b) (4) pressure forms a macrofoam.

MACROFOAM

1. The maximum time the drug formulation – CO₂-O₂ gas mixture remains in the polidocanol canister is 7 days as per the proposed in-use shelf life.
2. the oxygen canister is removed
3. the “microfoam transfer unit” (MTU) is attached to the polidocanol canister

MICROFOAM

1.  (b) (4)
2. 
3. 
4. 

INJECTION

1. foam is injected into the vein, displaces the blood in the vein and empties large veins of blood
2. echogenic with duplex ultrasound allows observation of the polidocanol injectable microfoam filling the targeted incompetent vein segment.
3. The foam lasts 75 sec.

REUSE

1. The MTU is removed
2. A new MTU is attached for the next treatment session following the steps above under MICROFOAM and INJECTION

Volumes of microfoam

1. 45mL of usable microfoam is produced
2. maximum injection of microfoam into the target vein in a single treatment session is 15ml.
3. typically, 2 to 10 mL of foam is injected into the great saphenous vein and 1 to 4 mL into the small saphenous vein
4. total dose of active sclerosant (i.e., 1.3 mg of polidocanol per 1 mL of polidocanol injectable microfoam 1.0%).

MATERIALS IN THE DEVICE

Version 4 is the proposed commercial presentation: a 2-canister (bi-can) product which is  (b) (4). The primary container closure system comprises of the following components (3.2.P.7 Page 8 of 44, 1.2. Component Details):

 (b) (4)

POLIDOCANOL SOLUTION CONTACTING THE DEVICE

The chemical interactions are operating under ambient conditions.

%w/w

The ingredients are commonly used elsewhere in the following applications:

1. Polidocanol 2-(dodecyloxy)ethanol $C_{14}H_{30}O_2$ MW 230
2. Ethanol
3. Disodium hydrogen phosphate (Na_2HPO_4) dihydrate (b) (4)
[Redacted]
[Redacted]
[Redacted]
4. Potassium dihydrogen phosphate (KH_2PO_4), aka Monopotassium phosphate or monobasic potassium phosphate (b) (4)
[Redacted]
[Redacted]
5. (b) (4)
6. Sodium Hydroxide Solution and 0.1 M Hydrochloric Acid Solution (HCl): Sodium Hydroxide (NaOH) aka lye or caustic soda (b) (4)

[REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]

However, NaOH is reacted with 0.1 M Hydrochloric Acid Solution (HCl) which results in a pH of 6.0-7.5.

CHEMICAL INTERACTIONS BETWEEN POLIDOCANOL SOLUTION AND THE DEVICE

O2 ALUMINUM CANISTER

[REDACTED] (b) (4)

POLIDOCANOL ALUMINUM CANISTER

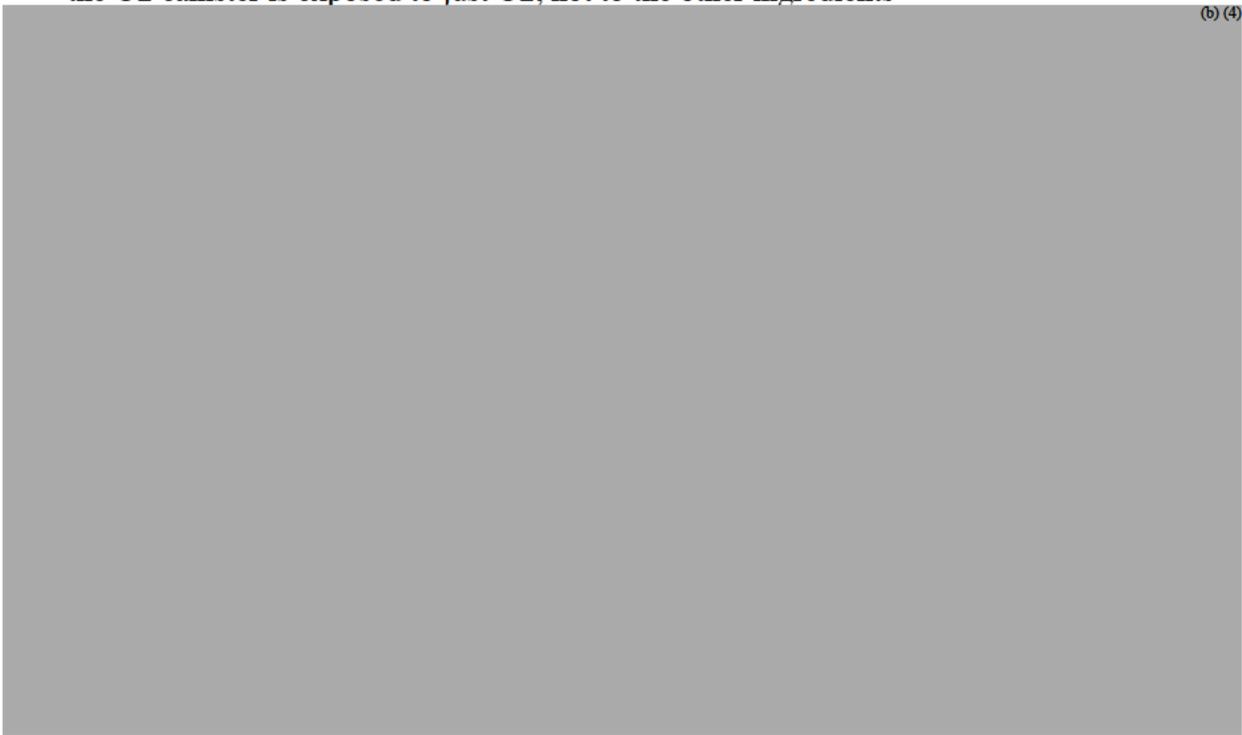
[REDACTED] (b) (4)

FOAM DELIVERY COMPONENTS

ADDITIONAL INFORMATION REQUESTED

1. Regarding the ingredients, please describe
 - a. the purpose of each ingredient
 - b. the chemical reactions that occur when mixed
 - c. the completeness of the reactions
 - d. amount of residue
 - e. the final pH
2. Regarding liquid storage in the aluminum canister in CO₂:
 - a. How long is the liquid stored before use?
 - b. What is the pH?

- c. Did you track the CO2 level during storage time?
 - d. How much oxygen residual is in the canister after long storage?
3. Regarding the O2 canister:
 - a. What is the purpose of the (b) (4) inside the O2 canister?
 - b. What is the (b) (4)?
4. Regarding the foam:
 - a. What is the foam temperature?
 - b. Is there cooling due to a drop in pressure?
 - c. What is the typical and maximum time of exposure of the parts to the foam?
5. The drug formulation – CO2-O2 gas mixture may remain in the polidocanol canister 7 days as per the proposed in-use shelf life. What is the rate of Aluminum Pitting corrosion and amount of metal ion release into the foam due to exposure of water and oxygen at this pressure 7 days?
6. Is the following a complete list of (b) (4) used in components of the device that are exposed to the polidocanol solution or foam? Note: The (b) (4) inside the O2 canister is exposed to just O2, not to the other ingredients



What (b) (4) may be exposed to the drug formulation – CO2-O2 gas mixture:

7 days as per the proposed in-use shelf life and

75 seconds during generation, dispensing and administering the microfoam

7. Provide methods and results to evaluate changes in surface chemistry of (b) (4) exposed to the polidocanol solution or foam that could affect performance such (b) (4)
8. What are the sterilization methods and effects on material properties, (b) (4)

FIRM'S RESPONSE

1 INGREDIENTS

THE PURPOSE OF EACH INGREDIENT Found in 3.2.P.1 , 3.2.P.2.1

THE CHEMICAL REACTIONS THAT OCCUR WHEN MIXED (b) (4)

(b) (4) 3.2.P.7

THE FINAL PH 6.0-7.5

2 LIQUID STORAGE

HOW LONG IS THE LIQUID STORED IN THE ALUMINUM CANISTER IN CO2 BEFORE USE? shelf life is 18 months

WHAT IS THE PH? 6.0-7.5 (b) (4)

DID YOU TRACK THE CO2 LEVEL DURING STORAGE TIME? (b) (4)

HOW MUCH OXYGEN RESIDUAL IS IN THE CANISTER AFTER LONG STORAGE?

This has not been measured. The Polidocanol Canister maintains a positive pressure during the long-term storage period.

3 O2 CANISTER

WHAT IS THE PURPOSE OF THE (b) (4) INSIDE THE O2

CANISTER? The purpose of the (b) (4)

WHAT IS THE (b) (4)? This has not been determined

4 FOAM

(b) (4)

5 CORROSION IN THE POLIDOCANOL CANISTER 7 DAYS AND METAL ION RELEASE INTO THE FOAM DUE TO EXPOSURE OF WATER AND OXYGEN

Stability (3.2.P.8.3) and compatibility (3.2.P.2.6) studies reported no adverse effect due to oxygen on the canister and aluminium below (b) (4)

(b) (4)

COMMENTS ON THE FIRM'S RESPONSE

1 INGREDIENTS

THE PURPOSE OF EACH INGREDIENT 3.2.P.1 , 3.2.P.2.1

THE CHEMICAL REACTIONS THAT OCCUR WHEN MIXED The (b) (4)

THE FINAL PH 6.0-7.5

2 LIQUID STORAGE

HOW LONG IS THE LIQUID STORED IN THE ALUMINUM CANISTER IN CO2 BEFORE USE? shelf life is 18 months

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DID YOU TRACK THE CO2 LEVEL DURING STORAGE TIME? (b) (4)

HOW MUCH OXYGEN RESIDUAL IS IN THE CANISTER AFTER LONG STORAGE?

This has not been measured. The Polidocanol Canister maintains a positive pressure during the long-term storage period.

3 O2 CANISTER

THE DIFFUSION RATE OF OXYGEN THROUGH THE (b) (4) is not needed now that it has been determined that the purpose is not to prevent oxygen diffusion.

Section 3.2.P.2, Page 49 of 189

4 FOAM

5 CORROSION IN THE POLIDOCANOL CANISTER 7 DAYS AND METAL ION
RELEASE INTO THE FOAM DUE TO EXPOSURE OF WATER AND OXYGEN

An adequate response was provided.

6 LIST OF MATERIALS An adequate response was provided.

7 CHANGES IN SURFACE CHEMISTRY (b) (4) EXPOSED TO
POLIDOCANOL

An adequate response was provided.

8 STERILIZATION METHODS AND EFFECTS ON MATERIAL PROPERTIES,
MINIMUM AND MAXIMUM STERILIZATION (b) (4)

An adequate response was provided.

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/s/

MICHAEL V MONTELEONE
10/23/2013



Department of Health and Human Services Memorandum

Food & Drug Administration
Center of Devices & Radiological Health
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: August 7, 2013

From: Jhumur D. Banik, M.S.
FDA/CDRH/ODE/PIDB

Subject: Engineering Consultant Review for **NDA 205098** (CDER)

Device Name: VarithenaTM (Polidocanol Injectable Microfoam)

Manufacturer: Provensis Ltd.
5 Fleet Place
London
EC4M 7RD
UK

Contact: Andreia Collier; Vice President, Regulatory Affairs

BACKGROUND

I was requested by Kenneth J. Cavanaugh, Jr., Ph.D. to review the functional properties of Provensis Ltd's container closure system that stores and helps generate the Polidocanol Injectable Microfoam (PD). Review for this portion of this submission began after the filing meeting held on March 14, 2013. On June 24, 2013, I was requested to review the microfoam test data by the CMC lead reviewer. Analysis of information reviewed until July 1, 2013 was discussed at the Mid-Cycle Meeting held on that day. Microbiological Ingress was not reviewed since that section is a part of the Microbiology review (Reviewer: Dr. Stephen Langille). Based on my review, the information provided is adequate to establish that container closure system functions as intended and that the device can consistently generate microfoam per the sponsor's specifications.

DEVICE PURPOSE

VarithenaTM (1.0% polidocanol injectable microfoam) is indicated for the treatment of incompetent great saphenous veins (GSVs), accessory saphenous veins, and visible varicosities of the GSV system above the knee and below the knee. This drug improves the symptoms of superficial venous incompetence and the appearance of visible varicosities in the GSV system.

PD is administered by injection directly into the lumen of the target incompetent veins and related varicosities of the great saphenous system (intravenously), using ultrasound guidance. The sponsor states that the maximum recommended volume per treatment session is 15mL; individual injections of up to 5 mL each. Also, based on the patient vein size, additional treatment sessions may be necessary. The proposed in-use shelf life for this product is seven days. The sponsor stated that the system is designed to generate sufficient polidocanol microfoam in a uniform and reproducible manner to treat several patients during the course of its proposed in-use shelf life.

Additional Deficiency Questions Addressed to Sponsor during Interactive Review:

During the review, additional questions were asked to the sponsor via email just to verify their specifications chosen for the microfoam analysis. The questions are as follows:

(b) (4)



RECOMMENDATION

Based on my review, the sponsor has provided sufficient information regarding their assembly process validation testing and testing for assessing the functional properties of the container closure system and for generating microfoam. Their performance testing demonstrated that the device design is capable of consistently producing foam with the same characteristics. In addition, the analytical procedures were appropriate to monitor the respective foam characteristics (i.e. half separation time, bubble size, and microfoam density). Therefore, **there are no concerns with the device design and microfoam generation.**

Jhumur D. Banik, M.S.
Biomedical Engineer, DCD/PIDB

Kenneth J. Cavanaugh, Jr. Ph.D.
Chief, DCD/VSDB

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/s/

MICHAEL V MONTELEONE
10/23/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: April 23, 2013

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID

THROUGH: Ron Kaye, MA, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID

CC: Molly Story, PhD, Human Factors and Accessible Medical Technology Specialist, DAGRID

TO: Mike Monteleone, Project Manager, CDER/OND/ODEI/DCRP

SUBJECT: NDA 205098
Applicant: BTG International
Device Constituent: VARISOLVE Microfoam Delivery System
(Canister, Transfer Unit, Syringe)
Intended Treatment: Severe Varicose Veins

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ron Kaye, Human Factors and Device Use-Safety Team Leader

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CDRH Human Factors Review

Combination Product Device Information

Submission Number: IND 63420

Applicant: BTG International

Drug Constituent: Varisolve Polidocanol Endovenous Microfoam (PEM)

Device Constituent: Canister Delivery System

Intended treatment: treatment of severe varicose veins

CDRH Human Factors Involvement History

- 23-Jan-2012: CDRH HF was first requested to provide a review on the Human Factors protocol contained in the IND
- 5-Mar-2012: CDRH HF provided one comment on assessing the interaction between the physicians and their clinical staff

Overview and Recommendation

The Division of Cardiovascular and Renal Products requested a consultative review from CDRH Human Factors team on the Human Factors (HF) study report (SP2277) for the Polidocanol Endovenous Microfoam (PEM) Drug Delivery device. This device consists of two canisters, (b) (4) and a microfoam transfer unit to facilitate the filling of the syringe. CDRH HF team was previously consulted to review the HF study protocol, where CDRH provided a comment on providing better characterization of the user tasks that will be performed by the physicians and their clinical staff, and assessing the interaction between the two user groups. The current submission includes a design risk analysis report and the Human Factors/usability validation study report. Review of this material identified one deficiency that should be transmitted to the Sponsor:

We note that you included the design risk analysis and the Human Factors/usability validation study report in the Risk Management Plan section of your submission. Your HF/usability validation study showed that there were a total of nine use errors, five close calls, 23 operational difficulties where three of the operational difficulties resulted in use errors with moderator intervention. Your analyses of study results and of use-related risks did not clearly describe the potential negative clinical consequences of the observed use errors/close calls/operational difficulties. In addition, we expect that the test results, and particularly failures or patterns of subjective reports of difficulty with the use of the device should be discussed with respect to whether they were caused by aspects of the design of the device, its labeling, the content or proximity of training, and whether modifications are required. Furthermore, your study conclusion stated that the “interpretation of whether this device is safe and effective to use must be made by BTG since they possess the clinical understanding of the impact of these use errors.” We expect that the conclusion should clearly state whether device is reasonably safe and effective for the intended users, uses, and use conditions. Please provide us the information the clinical consequences of the observed use errors/close calls/operational difficulties, and whether these results were caused by any aspects of the product design, labeling, and/or training, and whether modifications are required. Also, please provide your conclusion based on the study report results.

Human Factors Review

The study was conducted with 45 participants across three user groups (15 physicians, 15 clinical staff, and 15 staff assistants). The clinical staff and staff assistants were only responsible for preparing, setting-up the device, and inspecting the microfoam in the syringe. The physicians were responsible for preparation, inspecting, injecting into a manometer tubing within 75 seconds from the microfoam generation, and performing a final inspection of the microfoam through the manometer tubing. Training was provided to all test participants with a minimum of four hours training decay. There were a total of nine use errors, five close calls, 23 operational difficulties where three of the operational difficulties resulted in use errors with moderator intervention.

A total of nine use errors were committed by seven participants:

- One participant did not correctly initiate the gas transfer by twisting the wrong direction (counter-clockwise versus clockwise). As a result, the oxygen canister became stuck and the moderator had to provide the test participant a new device. The participant was then able to correct and initiate the gas transfer process. This same participant did not wait for one minute prior to removing the oxygen canister. The moderator intervened and asked the participant to refer to the Quick Reference Guide, and the participant realized the one minute wait time.
- Two participants were unable to remove the oxygen canister without the moderator intervention. One of the two participants was unable to accomplish the task due to physical limitations. The other participant tried to disengage the canister but stopped because it was in a locking position.
- Three participants did not write the first use date. One indicated that the task is not part of their normal tasks that they would perform, and would delegate it to their clinical staff. Two indicated that they forgot.
- Two participants did not inspect for presence of visible bubbles in the syringe. Both prepared additional syringe and created acceptable microfoam.

A total of five close calls were observed in the study:

- One participant initially placed the canisters on the counter top with the oxygen canister on the bottom instead of the top. The participant saw the arrows on the oxygen canister and realized that they had an incorrect orientation. The error was corrected during your gas transfer.
- Four participants committed close calls during the flushing step with the syringe, however, they realized and discarded the syringe, and used a new syringe with a new microfoam.

A total of 23 operational difficulties were observed in the study:

- Two participants experienced difficulties with initiating gas transfer task – one showed some difficulty but was able to complete the task; one could not move the oxygen canister into the locked position due to diminished hand strength.
- Five participants experienced difficulty regarding the force required to remove the oxygen canister but were able to complete the task.
- Eight participants had difficulty with aligning the MTU with the Polidocanol track but were able to complete the task. Another five participants had difficulty with the same task when setting up for a new patient.

Device Description

Table 1: Polidocanol injectable microfoam Operation Steps

(b) (4)



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Appendix 1: Previous CDRH Human Factors Protocol Review

DATE: March 15, 2012
FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID
THROUGH: Ron Kaye, MA, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID
CC: Molly Story, PhD, Human Factors and Accessible Medical Technology Specialist, DAGID
TO: Wendy Wilson, PhD, Chemist, CDER/OPS/ONDQA/DNDQAI
Teshara Bouie, Project Manager, OPS/ONDQA/DNDQAI
SUBJECT: IND 63420,
Applicant: BTG International
Device Constituent: VARISOLVE Microfoam Delivery System
(Canister, Transfer Unit, Syringe)
Intended Treatment: Severe Varicose Veins

Overview

The Division of New Drug Quality Assessment requested a Human Factors consultative review of the IND 63420 submitted by BTG International. In the cover letter dated 20-Feb-2012, the Applicant requests for comments and advice on the usability protocol and instructions for use before the pre-NDA meeting with the Agency scheduled on 26-Mar-2012. The VARISOLVE Polidocanol Endovenous Microfoam Delivery System is intended to treat patients with Severe Varicose Veins. This review provides CDRH's review and recommendations on the Human Factors related information contained in the IND. Please see the recommendation section for questions to be transmitted to BTG International.

Review Materials

Type B pre-NDA Meeting Request Package (dated 24-Feb-2012)
Usability Test Protocol PEM Delivery System (Draft, version 1.3, dated 8-Feb-2012)

Review of Human Factors Related Information

Device Description

The Polidocanol Endovenous Microfoam (PEM) system is used to create microfoam to treat an incompetent greater saphenous vein (GSV). The endovenous microfoam ablation (EMA) procedure is performed under duplex ultrasound, guidance and involves the injection of microfoam formulated from Polidocanol solution.

The Varisolve PEM drug/device combination product is provided as two canister system: one of the cans contains polidocanol held under a carbon dioxide atmosphere and the other can contains pressurized oxygen. The Varisolve PEM microfoam is generated via a pressurized canister, and transferred to a syringe through the Microfoam Transfer Unit (MTU) for delivery into the vein. The polidocanol active pharmaceutical ingredient (API), canister, and transfer system are all part of proprietary drug generation system.



Figure 1: Varisolve System (after Activation with Oxygen)

Summary of Human Factors/Usability Test Protocol

The product is shipped to the uSer in the form of a two-canister system. One canister contains the Polidocanol solution and carbon dioxide gas, and the other canister contains oxygen. When the contents of the two canisters are connected and activated the pressures equalize. These canisters have a connector unit, which keeps them separated during shipment and allows for easy transfer of the oxygen into the Polidocanol canister prior to use.

Description of User Interaction

Once the oxygen transfer into the Polidocanol canister is initiated, the user waits one minute then separates the canisters. A Microfoam Transfer Unit (MTU) is then mounted on the Pondocanol canister to complete the PEM delivery system. (b) (4)

When generating the microfoam, the user must prime and flush visible bubbles from the MTU and the syringe in order to produce a syringe full of usable microfoam. The microfoam is dispensed from the MTU into (b) (4) syringes, which are then utilized in the EMA procedure.

Once microfoam is created, the physician must inject it into the greater saphenous vein (GSV) or other selected vein via a manometer tube - placed earlier in the procedure - within 75 seconds of creation. If any visible bubbles are seen in the manometer tube, the physician should stop the injection, aspirate the visible bubbles back into the syringe, and discard its contents.

The PEM Polidocanol canister is a multi-access product, able to produce 3 (three) 5mL doses of microfoam per treatment. A total of 3 treatments can be done from one canister. A new MTU must be used for each patient/treatment.

Intended Users

The intended users for this product can be broken down into two user groups: physicians and clinical staff that provide treatment for varicose veins. The clinical staff includes a scrub nurse, a circulating nurse, and a duplex ultra-sonographer. BTG International plans to recruit 20 physicians and 20 clinical staff for the study.

Device Use Environment

The typical use environment for the proposed product includes physician's office suite and/or hospital setting. The simulated use environment will represent realistic use environment.

Previous Human Factors Evaluations

BTG International have conducted several exploratory evaluations to develop and refine the Instructions for Use, and to implement measures to improve device design.

User Task Selection

Based on use-related risk analysis, and exploratory evaluations, the follow tasks have been determined to have critical influence on the safe and effective use of this device:

- Gassing of Polidocanol canister (oxygen transfer into Polidocanol canister)
- Attachment of MTU
- Generation of microfoam
- Inspection of Microfoam
- Changing of MTU

Data Collection and Analysis

Subjective and performance data will be collected during the study. Subjective data will include study participants feedback on use errors, close calls, and general difficulties. Performance data will focus on the defined critical use tasks including gas transfer time, hold time after transfer, microfoam use time, and visual inspection for visible bubbles.

Training

Upon product commercialization, training on the entire clinical procedure including product preparation, unique clinical procedures and interventions, and patient post-procedure activities will be provided to physicians and their staff. For the simulated use study, participant training will be limited to the information required to interact with the delivery system. Training on in vivo procedures will not be included. A product demonstration and a walk-through of the training materials including IFU will be provided to test participants. In addition, test participants will be asked to perform the gas transfer, attach the MTU, generate microfoam, inspect the microfoam for visible bubbles, and inject microfoam into the manometer tubing while inspecting for visible bubbles. There will be a minimum of a 4 hours delay before testing will be introduced.

Review Recommendations

Overall, the proposed protocol appears adequate in terms of study methodology for:

- Defining the intended user population and extent of training necessary for the use of the product,
- Identifying simulated use environment that represents realistic use environment,
- Prioritizing and identify critical tasks based on risk assessment, and

- Collecting and analyzing the necessary data to demonstrate safe and effective use.

This protocol presents an interesting use scenario for which both the physicians and their clinical staff will be participating in the simulated use study. Based on the information presented in the study, it is unclear if physicians and clinical staff will have similar tasks or have specific and different task sets. It is also not clear whether or not the interaction between physicians and their clinical staff is critical in safe and effective use. In addition, a use-related risk analysis was not provided along with the Human Factors/usability validation study protocol. The Applicant should be asked to provide this analysis along with the rationale for the task selection for the study.

Please transmit the following comments to BTG International:

This protocol presents an interesting use interaction for which both the physicians and their clinical staff will be participating in the simulated use study as two separate user groups. However, when you referred to the “user” in the protocol, it is unclear if you refer to either the physicians and/or clinical staff. Please clarify whether physicians and clinical staff will perform similar tasks or have specific yet different task sets. Please provide a task and function analysis for the two intended user groups. Please also clarify whether the interaction between physicians and their clinical staff while using the device is critical in safe and effective use.

In addition, a use-related risk analysis was not provided along with the Human Factors/usability validation study protocol. Please provide this analysis along with the rationale for the task selection and inclusion in the study.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

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/s/

MICHAEL V MONTELEONE
10/23/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: October 31, 2013

To: Michael Monteleone, Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

From: Emily Baker, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 205098**
OPDP Labeling Comments for Varithena (polidocanol injectable microfoam)

OPDP has reviewed the proposed carton and container labeling submitted for consult on October 29, 2013, for Varithena (polidocanol injectable microfoam) (Varithena). Our comments are based on the proposed labeling emailed to us on October 24, 2013.

OPDP has no comments on the proposed carton and container labeling at this time.

Thank you for the opportunity to comment on the proposed materials.

If you have any questions, please contact Emily Baker at 301.796.7524 or emily.baker@fda.hhs.gov.

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/s/

EMILY K BAKER
10/31/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Usability Study, Label, Labeling, and Packaging Review

Date: October 1, 2013

Reviewer: Kimberly DeFronzo, RPh, MS, MBA
Division of Medication Error Prevention and Analysis

Team Leader: Irene Z. Chan, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Drug Name and Strength(s): Varithena (Polidocanol) Injectable Microfoam
1%

Application Type/Number: NDA 205098

Applicant/sponsor: Provensis Ltd.

OSE RCM #: 2013-486 and 2013-487

*** This document contains proprietary and confidential information that should not be released to the public. ***

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1 INTRODUCTION

This review responds to a request from the Division of Cardio-Renal Products (DCRP) to evaluate the results from the validation usability study SP2277 and the proposed labels and labeling for Varithena Polidocanol Injectable Microfoam.

We previously reviewed the Applicant's usability study protocol under IND 063420 (see OSE RCM #2012-529 dated May 21, 2012).

1.1 PRODUCT INFORMATION

The Applicant provided the following product information on May 1, 2013.

- **Active Ingredient:** Polidocanol
- **Strength:** 1%
- **Indications:** For the treatment of incompetent great saphenous veins, accessory saphenous veins and visible varicosities of the great saphenous vein (GSV) system above and below the knee. Varithena improves the symptoms of superficial venous incompetence and the appearance of visible varicosities in the GSV system.
- **Route of Administration:** Intravenous
- **Dosage Form:** Microfoam
- **Dose and Frequency:** Varithena is intended for intravenous injection using ultrasound guidance, administered via a single cannula into the lumen of the target incompetent trunk veins or by direct injection into varicosities. The maximum recommended microfoam volume per treatment session is 15 mL, divided into aliquots of up to 5 mL.
- **Description:** Varithena is a microfoam of aqueous polidocanol and a gas mixture consisting of oxygen and carbon dioxide. The solution is stored under a carbon dioxide atmosphere in an aluminum canister prior to use. This canister is activated with oxygen from a second canister to result in a final gas mixture of oxygen: carbon dioxide in a ratio of 65:35 with low nitrogen content. At the time of use, the Varithena is generated via the container system that produces microfoam of controlled density and bubble size. The microfoam is then transferred to a syringe through a MTU. Varithena delivers polidocanol at solution concentration of 1.0% weight per volume. The microfoam density has a volume of liquid to gas ratio of approximately 1:7. The median bubble diameter is less than 100 µm and no bubbles are greater than 500 µm.
- **How Supplied:** Varithena is supplied in a convenience box that contains:
 - A Tyvek pouch containing two sterile, connected 303 mL aluminum alloy canisters: one containing (b) (4) Polidocanol Solution under a carbon dioxide atmosphere, the second containing pressurized Oxygen at approximately 5.4 bar absolute. The Connector joins the two canisters and activates the product.

A canister of Varithena generates 90 mL of microfoam which, following purging instructions contained in the IFU, is sufficient to yield 45 mL of usable microfoam for injection
 - Three Microfoam Transfer Units to dispense microfoam

- Three administration boxes each containing:
 - Three 10 mL silicone-free Luer syringes
 - A 20-inch Manometer Tube
 - Two Compression Pads
- **Distribution:** Will be supplied directly to physician’s offices, hospitals, and clinics that have received the certificate training from the Applicant. Following enrollment and completion of the online training program, physicians will be notified and automatically be entered into the PEM commercial distribution database, allowing access to PEM. The physician will be given the option to schedule live in-office support as needed for hands on training.
- **Storage:** Store the Varithena convenience box at 68° to 77°F (15° to 25°C); excursions are permitted to between 59° to 86°F (15° and 30°C). Do not refrigerate or freeze.

2 METHODS AND MATERIALS REVIEWED

DMEPA evaluated the results from validation usability study SP2277 and the proposed labels, labeling, and packaging design for Varithena Polidocanol Injectable Microfoam.

2.1 USABILITY STUDY

We reviewed the Design Risk Analysis Report that provides the results of Validation Usability Study SP2277 submitted by the Applicant on February 4, 2013 (see Appendix A).

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, we evaluated the following:

- Polidocanol Canister Label submitted on September 24, 2013 (Appendix A)
- Oxygen Canister Label submitted on September 24, 2013 (Appendix B)
- Administration Box Labeling submitted on September 24, 2013 (Appendix C)
- Bi-Canister Box Labeling submitted on September 24, 2013 (Appendix D)
- Bi-Canister Pouch Labeling submitted on September 24, 2013 (Appendix E)
- Commercial Presentation Carton Labeling submitted on September 24, 2013 (Appendix F)
- Microfoam Transfer Unit (MTU) Labeling submitted on September 24, 2013 (Appendix G)
- Insert Labeling submitted on May 1, 2013 (no image)
- Instructions for Use submitted on August 28, 2013 (no image)

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 RESULTS

The following sections describe the results of our risk evaluation of the validation usability study as well as the labels, labeling, and packaging for Varithena.

3.1 USABILITY STUDY

3.1.1 Study Design

The primary objective of the study was to validate that intended users of the Varithena (Polidocanol) Endovenous Microfoam Delivery System can safely and effectively perform the critical tasks to generate microfoam for treatment of varicose veins.

Summative validation testing was conducted with 45 participants (15 physicians, 15 clinical staff, and 15 staff assistants), all of who currently treat varicose veins. Participants were provided with hands-on training. There was a minimum of 4 hours between training and usability testing to allow for memory decay. Participants were then asked to prepare the microfoam as taught during their training session. Once microfoam was generated, the clinical staff and staff assistant participants were required to inspect the microfoam then hand the syringe to the moderator, whereas the physician participants were asked to further conduct a simulation of the inspection of microfoam and simulated injection into manometer tubing, including final inspection of the microfoam through the manometer tubing during injection. Each participant was randomly assigned to prepare one to three doses during testing.

The Applicant identified a total of 13 critical tasks that all participants need to perform in order to generate microfoam. Physician participants had 3 additional critical tasks (total 16 critical tasks) that they needed to perform in order to inject the microfoam (see Table 1 below). The 45 participants prepared a total of 80 doses.

3.1.2 Study Results

The Applicant reported 9 use errors (committed by 7 participants), 5 close calls, and 23 operational difficulties observed (in 3 cases of observed operational difficulty this resulted in use errors²). However, further examination of all of the information submitted by the Applicant, including the risk analysis and results table beginning on page 127 of 176 in the Design Risk Analysis Report, identified additional use errors. Additionally, in some areas of the report, the information was contradictory or inadequately explained. Table 1 below shows the results of our independent analysis of the cumulative data included in the study report.

Table 1. Observed Use Errors, Close Calls, and Operational Difficulty in Study SP2277					
Critical Task	Potential Use Errors	Observed Use Errors	Close Calls	Operation Difficulty	Description/Root Cause Analysis of Use Error or Close Call
Removing the safety clip	45	0	0		
Canisters in correct orientation for gas transfer (oxygen)	45	0	1		Participant initially placed oxygen canister on bottom but realized their mistake and self-corrected the orientation. No contributing factor was reported.

² These 3 use errors are already included in the 9 use errors identified by the Applicant.

canister on top)					
Initiating gas transfer (twisting the oxygen canister to the locked position)	45	2	0	3	<p>One participant twisted the oxygen canister counter-clockwise instead of clockwise, resulting in the canister becoming stuck and required a restart with new canisters. When further questioned, the participant indicated they thought they had turned the canister clockwise, but realized there was an issue when the canister was stuck.</p> <p>A second participant had operational difficulty, and twisted the canister correctly but did not manage to get it into the “locked” position. This particular participant had compromised hand strength due to severe arthritis and a previous broken thumb.</p>
Waited 1 minute for gas transfer	45	1	0		<p>The same participant that twisted the oxygen canister counter-clockwise instead of clockwise (see row above) immediately removed the oxygen canister after twisting the two canisters together. This participant stated that the initial use error related to initiating gas transfer was disorientating and he became flustered and forgot which step was being performed, which led to this second use error.</p>
Removing the oxygen canister	45	2	0	7	<p>One participant had compromised hand strength due to severe arthritis and a previous broken thumb (this same participant was also unable to initiate the gas transfer).</p> <p>The second participant attempted to disengage the oxygen canister from the polidocanol canister but was unable to remove the oxygen canister. The participant stated he/she was afraid to use more force since it may damage the canister.</p>
Write first use date directly on canister	45	3	0		<p>One participant was a physician who stated he/she forgot since this is not a normal task they would perform as this task would be left to the clinical staff. This physician did say he/she would write the date if they were doing this by him/herself.</p> <p>The second participant was a nurse that stated that he/she forgot to do this task since being watched made him/her nervous.</p> <p>The third user was also a nurse who stated “yeah, literally, I forgot to date it.”</p>
Attaching the MTU	45	0	0	8	
Priming the syringe	80	5	0		<p>On page 161 or 176, the Applicant indicated “5 deviations” were observed. From what we gathered, in 2 out of a possible 80 doses drawn during the study, the participant did not depress the MTU long enough to fill the syringe between 3 mL and 5 mL for priming. No contributing factors were reported.</p> <p>In 2 out of a possible 80 doses drawn during the study, participants did not depress the syringe plunger fully to discard the syringe contents prior to the flushing and generating usable microfoam. No contributing factors were reported.</p> <p>It is unclear what occurred in the fifth “deviation” noted by the Applicant.</p>
Flushing (purge cycle)/filling the syringe	80	4	4		<p>The Applicant identified four close calls where the participants identified that a mistake had occurred and restarted the task without prompting from a moderator. In 2 of the close calls, the syringe plunger was not held in place during the flushing (purge cycle) to allow for observation of microfoam bubbles. No contributing factors were reported. In the other 2 close calls, the MTU was prematurely released before syringe filling could begin. No contributing factors were reported.</p> <p>In 4 out of a possible 80 doses drawn during the study, the participant overfilled the syringe because they did not hold the syringe plunger in place to prevent filling past the desired volume (dose). No contributing factors were reported.</p>
Inspect syringe for proper microfoam	80	2	0		<p>Two doses were prepared and handed to the moderator with small visible bubbles in the syringe. Both participants (1 medical assistant</p>

(presence of bubbles)					and 1 clinical assistant) did inspect the syringe but did not see the bubbles.
Microfoam handed within 45 seconds (Staff Only)	49	0	0		
Inspect Manometer for Proper Microfoam (Physicians Only)	31	0	0		
Reject Unacceptable Microfoam in Manometer if Needed [Physician Only]	6	0	0		
Microfoam Used within 75 seconds of Generation (Physicians Only)	31	0	0		
Removing Used MTU	45	0	0		
Attaching New MTU for a new patient	45	0	0	5	
Total	----	19	5	23*	

*Out of the 23 operational difficulties observed, 3 resulted in user errors

3.2 PACKAGING, PRODUCT COMPONENTS, CONTAINER CLOSURE

The following sections discuss the results of our risk assessment of the packaging and product components.

3.2.1 Components of Commercial Carton

Our review of the items contained within the commercial carton determined that the carton provides adequate supplies to treat up to three different patients for three separate treatment sessions (up to 15 mL administered in 3 x 5 mL aliquots, if needed, for each treatment session). This is consistent with the proposed insert labeling and Instructions for Use (IFU) for this product. Therefore, we have no recommendations regarding the contents of the commercial carton.

3.2.2 Risk Assessment of Syringes

The Applicant did not implement one of DMEPA's previous recommendations³ to replace the 10 mL syringe with a 5 mL syringe to minimize the risk of overdose (i.e. giving greater than a 5 mL aliquot). The Applicant stated in an Information Request (IR) response that the use of a 5 mL syringe would result in very rapid filling which may cause the plunger to be expelled from the syringe. In addition, the user must account for the dead space in the manometer tube, intravenous access catheter, and other connections between the syringe and the patient during. The ONDQA reviewer agreed with the Applicant's rationale in support of a 10 mL syringe. Additionally, the DCRP medical officer did not have clinical concerns since there is data supporting the safety of this product when up to a 60 mL dose

³ See OSE review #2012-529 dated May 21, 2012

was used in patients during the clinical trials. Therefore, based on the Applicant's response and input from the DCRP medical officer and ONDQA reviewer, we find the 10 mL syringes acceptable.

We note that the syringes are described as "silicone-free" in the Information Request response; however, in the IFU, the syringes are described as "low-silicone". The Applicant will need to reconcile this discrepancy and ensure the IFU and all labels and labeling reflect the correct information.

3.2.3 Labels and Labeling

Our risk assessment of the proposed labels and labeling identified areas of concern which can be improved for clarity, to increase the readability and prominence of important information on the labels, and to promote the safe use of the product. We provide recommendations in Section 4 below.

3.3 INTEGRATED MEDICATION ERROR RISK ASSESSMENT

Our review of the results from validation usability study SP2277 and evolving information during this application cycle has determined that the Applicant has not demonstrated usability of the intended commercial version of this combination product. However, preliminary feedback from DCRP suggests that the benefits of this product compared to available options currently on the market outweigh the potential risks associated with this combination product. Therefore, with the anticipated approval of this product, DMEPA will provide recommendations to address the failures seen in the usability study.

Our analysis of the usability data submitted by the Applicant determined there were 19 use errors that occurred during the study. Of the 19 use errors, 5 occurred with initiating gas transfer, waiting for gas transfer, and removal of the oxygen canister. There were also 10 operational difficulties reported with initiating gas transfer, waiting for gas transfer, and removal of the oxygen canister. Additionally, there were 8 operational difficulties reported with attaching the MTU to the canister. DMEPA also identified operational difficulty with the sample canisters submitted to the Agency, which we found difficult to twist and assemble. The root cause analysis suggested that users with compromised hand strength or dexterity may encounter difficulty with using this product. The Applicant subsequently provided new commercial grade versions of the canisters which appear to demonstrate improvement in ease of assembly, twisting, and removal of the oxygen canister. However, it does not appear that the intended-to-market version was validated in usability study SP2277. If we identify continued difficulty with gas transfer, removal of the oxygen canister or MTU attachment during postmarket surveillance, the Applicant may need to investigate and make further design changes to the device itself since we do not believe the user errors and operational difficulty can be mitigated through labels and labeling.

In 3 of the 19 use errors, participants did not write the first use date directly on canister. The root cause analysis performed in the study indicated that participants forgot to perform this step, or in one case, the participant did not consider this a task they would normally perform. We do not consider this a failure that is likely to be impacted by a change in device design. Therefore, we recommend bringing attention to this task in the Instructions for Use (IFU). We also recommend increasing the prominence of the "date and time of activation" box on the polidocanol canister label and adding an additional statement to the bi-canister pouch labeling and commercial carton labeling reminding users of this task.

In 11 of the 19 use errors, failures occurred during priming, flushing/filling the syringe, and inspection of microfoam. However, the root cause analysis performed did not identify contributing factors. Since device design changes are not feasible at this point in time, we will provide recommendations for bringing additional prominence to specific instructions and provide clarity in the IFU.

Since the validation usability study was conducted, numerous changes have been made to the IFU that have not been validated. A new critical task of swabbing the uncovered shuttle with a fresh sterile alcohol wipe when replacing the MTU was also added due to sterility concerns when changing the MTU between patients. This task was never evaluated in a usability study. Additionally, during study SP2277 hands-on training was provided for all study participants. The Applicant initially proposed (b) (4)

DMEPA recommends the Applicant broaden their training program, both online and in person, to include all users. However, even with expanded training, it is unclear how the changes to the device, labeling, and training will impact the usability of the product. Therefore, if we identify failures during postmarket surveillance, the Applicant may need to investigate and make further design changes to the device, labels, labeling, or packaging.

4 CONCLUSIONS AND RECOMMENDATIONS

Our review has determined that the Applicant has not demonstrated usability of the intended commercial version of this combination product. However, we recognize the proposed product has advantages over the current available therapies and may offer benefits that outweigh the risk of device failures. Therefore, we provide recommendations for the Instructions for Use (IFU) to add clarity and bring prominence to specific information that will further minimize the risk for use errors.

We conclude that the proposed labels and labeling can be improved to provide clarity and increase the readability and prominence of important information on the label to promote the safe use of the product. DMEPA advises the following recommendations be implemented prior to approval of the application.

If you have further questions or need clarifications, please contact Cheryle Milburn, OSE Project Manager, at 301-796-2084.

4.1 COMMENTS TO THE DIVISION

A. General Comment Regarding Usability

Physicians will not be the only end users for this product and it is unclear how other healthcare professionals will receive training. DMEPA recommends the Applicant broaden their training program, both online and in person, to include all users.

B. Insert Labeling

1. Under section 2 Dosage and Administration, we recommend adding additional language to the sentence “Use a new sterile syringe after each injection” such as “Use only the syringes enclosed in the kit to ensure maximum foam integrity.”
2. Under section 2 Dosage and Administration, consider revising the statement (b) (4)
3. We recommend avoiding dangerous abbreviations or symbols, such as hyphens or the symbols $>$ and \leq , and adding units of measure, where applicable, to numbers throughout

the insert labeling. For example, “3-5 cm” would be revised to read “3 cm to 5 cm” under the Dosage and Administration section 2 of the Full Prescribing information.

4. Section 16 *How Supplied* lists the syringes as “Three 10 mL *silicone-free* Luer syringes”. This differs from the description found in the IFU of “*low-silicone* syringes”. We recommend clarifying which presentation is accurate and updating all labels and labeling for consistency.

4.2 COMMENTS TO THE APPLICANT

A. General Comments for All Labels and Labeling

1. Ensure the NDC is located in the upper one third of the principal display panel as per CFR 207.35(3)(i).
2. The proprietary name, established name, and strength should be removed from all panels of labels and labeling of components that do not contain polidocanol. Instead, the labels and labeling should clearly indicate what the component is. A statement can be added to indicate that the component is to be used only with Varithena (polidocanol) Injectable Microfoam, but this statement should not be the most prominent statement on the label.

B. Polidocanol Canister Label (see Appendix B):

1. Ensure the established name (which includes the dosage form) is at least ½ the size of the proprietary name taking into account typography, layout, contrast, and other printing features and has prominence commensurate with the proprietary name as per 21 CFR 201.10(g)(2).
2. Move the route of administration statement “For Intravenous Use Only” directly beneath the established name and strength. Additionally, increase its prominence through bolding or font size.
3. Increase the prominence of the statement of strength “1%” by increasing the font size and removing the “(b) (4)” from the color circle since the dosage form is already present as part of the established name.
4. Debold the “Rx Only” statement and decrease the font size.
5. Increase the prominence of the statement “Date and time of activation:” as well as the box underneath through the use of font size, bolding, color, or other means to avoid inadvertent use of an expired product.

C. Oxygen Canister Label (see Appendix C)

1. To clarify the purpose of this canister and encourage its proper use, we recommend adding to the principal display panel a statement such as “Does Not Contain Drug. Must be mixed with Attached Polidocanol Canister. See instructions for use.”
2. To avoid confusion that this canister contains drug substance, remove the statement (b) (4)
3. See comment B4 above.

- D. Bi-Canister Pouch Labeling (see Appendix E)
1. We recommend including a statement similar to “Write the date and time of activation on the Varithena canister after first use.”
 2. For clarification, revise [REDACTED] ^{(b) (4)} to read “One canister of Varithena contains: 180 mg...”
 3. Remove the trailing zero in 1.0% so it reads 1%.
 4. See comments B1, B3, and B4 above.
- E. Bi-Canister Carton Labeling (see Appendix D)
1. See recommendations B1, B3, B4, D2, and D3 above.
- F. Administration Box Label (see Appendix C)
1. Increase the prominence of the statement “A new box must be used for each patient” by increasing the font size, using a different font color, bolding, boxing, or some other means. Additionally, move this statement above the “Contents” information.
 2. See comment B4 above.
- G. Commercial Presentation Carton Labeling (see Appendix F)
1. See comments B1, B3, and B4 above.
 2. Increase the prominence of the statement “For Dosage and Administration read the PI and IFU” by increasing the font size, bolding, and moving the statement above the “Contents”. Additionally, for improved clarity, replace the abbreviations “PI” and IFU” with the full intended meanings, “Package Insert” and “Instructions for Use”.
 3. Combine the separate “Contents” sections into a single section that includes the polidocanol canister, the oxygen canister, 3 x microfoam transfer units, and 3 x administration boxes. Additionally, if feasible, the contents should also reflect what is contained in each administration box.
 4. We recommend including a statement similar to “Write the date and time of activation on the Varithena canister after first use.”
- H. Microfoam Transfer Unit (MTU) Lid Labeling (see Appendix G)
1. Increase the prominence of the statement “A new MTU must be used for each treatment session.” by increasing the font size, bolding, and moving the statement above the “Contents”. Additionally, we recommend also stating “Use aseptic technique when handling MTU.”
- I. Instructions for Use (IFU)
1. On the cover page, bold the statement “Always write the activation date...use.” Additionally, move this statement above the “Rx Only” statement for increased prominence.
 2. We recommend adding a picture of alcohol swabs to Figure 1b under the “Unpacking” section.

3. Under the current Step 6, we recommend revising the statement “Write today’s date and time...” to read “Write today’s date and time in the “Date and time of activation” box on the Varithena canister label. Additionally, we recommend bolding this instruction and moving it above figures 9 and 10 for increased prominence.
4. Under Step 8, bold the statement “Using continuous pressure...5 mL.”
5. Under Step 10, we recommend boxing the “Important Note: Microfoam...” statement.
6. Under Step 12, bold the words “inspect it for visible bubbles”.
7. Under Step 14, bold the statement “Do not remove the MTU if...” to ensure proper storage.
8. We recommend increasing the prominence (by bolding, etc.) of the statement “Swab the uncovered shuttle with a fresh sterile alcohol wipe” in Step 17 to draw attention to this important step.

6 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Appendix H: Complete response from Applicant to DMEPA Information Request

Provensis believes that the 10mL syringes are appropriate for use with the Polidocanol Injectable microfoam based on the following:

- During the generation of the microfoam, as the syringe is filled by pressure in the canister, reducing the bore of the syringe and volume would result in very rapid filling and the potential for the plunger to be expelled from the syringe. This step is unique to the Polidocanol Injectable Microfoam, and the syringe size is key to provide the Healthcare Professional with the control that is required. With a 10 mL syringe, the fill is steady and can be terminated close to but in excess of the required volume and the syringe contents then adjusted precisely by injecting any excess back into the Microfoam Transfer unit.
- In accordance with our proposed prescribing information, the maximum recommended microfoam volume per treatment session is 15 mL, divided into 3 aliquots, and cannot be exceeded with a single injection using a 10mL syringe.
- For the administration of the microfoam, whilst the maximum single injection volume into the vein is 5 mL, the Healthcare Professional must account for the deadspace in the manometer tube, intravenous access catheter and other connections between the syringe and the patient during administration. This could not be achieved with the use of a 5 mL syringe.

We have substantial experience with the use of 10 mL syringes as it is the same type of syringe used in the pivotal phase 3 clinical studies. During clinical studies, the proposed syringe has been shown to be suitable for ease of use and handling of product during the procedure.

In regard to DMEPA's concerns about a possible overdose error, Provensis can confirm that there were no reported instances of administration of inappropriately large volumes of Polidocanol Injectable Microfoam. The maximum volume of Polidocanol Injectable Microfoam per treatment session recommended for licensure is 15 mL. As documented in the Clinical Overview provided in the original NDA, in previous clinical studies, up to 60 mL per treatment session, or up to 4 times the maximum volume recommended, has been safely administered.

In addition, the absolute quantity of polidocanol delivered per treatment is markedly lower with Polidocanol Injectable Microfoam compared with liquid polidocanol. The maximum dose specified in the Asclera® PI (NDA 21,201) is 10 mL of 1% solution, which contains 100 mg of polidocanol (Merz Aesthetics, Inc. 2010, reference provided in NDA). In contrast, the maximum volume of Polidocanol Injectable Microfoam 1.0% proposed for licensure, 15 mL, contains 19.5 mg of polidocanol or less than one-fifth of the polidocanol in the maximum dose of Asclera®. Therefore, administration of a full syringe of 10 mL of microfoam (containing 13 mg of polidancol) does not present a risk of overdose of polidocanol.

Taking into consideration the rationale presented above as well as the recommendation made by DMEPA to reduce the size of the syringe, Provensis has concluded that the 10 mL syringe is the appropriate syringe for use for the generation and administration of the Polidocanol Injectable Microfoam without risk of overdose.

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

/s/

KIMBERLY A DE FRONZO
10/01/2013

IRENE Z CHAN
10/01/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: June 28, 2013

TO: Khin Maung U, Medical Officer
Michael Monteleone, Regulatory Project Manager
Division of Cardio-Renal Drug Products

FROM: Sharon K. Gershon, Pharm. D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 205098

APPLICANT: BTG International Inc.

DRUG: Polidocanol Injectable Microfoam (Varithena™),
formerly called PEM (polidocanol endovenous microfoam) or
Varisolve®

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: Treatment of incompetent great saphenous veins (GSV), accessory saphenous veins, and visible varicosities of the GSV above and below the knee and improvement of the symptoms of superficial venous incompetence and the appearance of visible varicosities in the GSV system

CONSULTATION REQUEST DATE: February 15, 2013

INSPECTION SUMMARY GOAL DATE: September 4, 2013

DIVISION ACTION GOAL DATE: December 4, 2013

PDUFA DATE: December 4, 2013

I. BACKGROUND:

The sponsor BTG International, Inc. is seeking approval for polidocanol injectable microfoam (formerly called polidoconal endovenous microfoam PEM) as a treatment for incompetent veins of the GSV system, including improvement of symptoms of superficial venous incompetence of the GSV system and appearance of visible varicosities of the GSV system. The Sponsor has conducted three Phase 3 studies of PEM in the U.S.: Study VAP.VV015, Study VAP.VV016, and Study VAP.VV017. Studies 015 and 016 are the pivotal trials for this indication.

Chronic venous insufficiency of the lower extremities is commonplace in adults. The prevalence depends on a number of factors including age, gender, family history, geographic location, pregnancy and obesity. One study has shown nearly 30% of the population to have visible disease involving varicose veins or trophic changes of the legs, and 28% of the population to have functional disease of either the major superficial or deep leg veins. Besides appearing as abnormal, patients can suffer pain, alterations in skin pigmentation, inflammation, induration, and skin ulceration as a result. Treatment options have largely consisted of use of hosiery for compression, conventional surgical ligation or venous stripping, subfascial endoscopic perforator surgery, endovenous laser ablation, radiofrequency ablation, and chemical sclerotherapy. In recent years the use of foamed sclerosants has become increasingly popular, largely because foam instillation confers a homogeneous distribution within the vessel lumen, and controllable duration of effect.

Polidocanol is the most commonly used foam sclerosing agent in Europe and is the only sclerosant approved by the Japanese Ministry of Health, Labor and Welfare. Polidocanol is not approved by the United States Food and Drug Administration (FDA), but it has been studied extensively in completed and ongoing Phase II and Phase III studies within and outside the United States.

Subjects in the studies were administered study drug or placebo endovenously in 1 or 2 treatment sessions 1 week apart. Following Visit 5 (Week 8), subjects could have 1 or 2 optional, open-label treatment sessions with PEM 1.0%, 1 week apart.

The primary efficacy endpoint of Studies 015 and 016 was the absolute change of the 7-day average electronic daily diary (e-diary) Varicose Vein Symptoms Questionnaire (VVSymQ) score at Week 8 in patients treated with PEM at various strengths compared to Vehicle. The daily VVSymQ score was the sum of the duration scores for each of five symptoms (heaviness, achiness, swelling, throbbing, and itching) and ranged between 0-25 points.

The co-secondary efficacy endpoints related to appearance:

1. Independent Photography Review – Visible Varicose Veins (IPR-V³) score (assessed by trained, blinded physicians), and
2. Patient Self-assessment of Appearance of Visible Varicose Veins (PA-V³) score (assessed by the patient).

Protocols:

No. VAP.VV015, entitled “A Randomized, Blinded, Multicenter Study to Evaluate the Efficacy and Safety of Varisolve[®] Polidocanol Endovenous Microfoam (PEM) 0.5%, 1.0%, and 2.0% Compared to Vehicle for the Treatment of Saphenofemoral Junction Incompetence”

No. VAP.VV016, entitled “A Randomized, Blinded, Multicenter Study to Evaluate the Efficacy and Safety of Varisolve[®] Polidocanol Endovenous Microfoam (PEM) 0.5% and 1.0 % Compared to Vehicle for the Treatment of Saphenofemoral Junction Incompetence”

II. RESULTS (by Site):

Five U.S. sites were selected to inspect for NDA 205098. These sites were selected because they enrolled large numbers of subjects, showed strong positive results, or had a relatively large number of protocol violations. In addition, some sites had a large number of subject discontinuations and subjects who were excluded from the efficacy analysis. The review division provided a table of specific data to be verified during inspections at each site. FDA field investigators addressed the applicable issues during their inspections (see Inspectional Results below).

Name of CI	Protocol #, Site # and # of Subjects	Inspection Dates	Final Classification
Kenneth Deck 24411 Health Center Dr. Laguna Hills, CA 92653	VAP.VV015 Site #39 37 subjects	March 26 – April 3, 2013	VAI
Ariel Soffer 17901 NW 5th Street Pembroke Pines, FL	VAP.VV015 Site #37 35 subjects	April 9 – 11, 2013	NAI
Brian Ferris 12333 NE 130th Lane, Kirkland, WA 98034	VAP.VV015 Site #33 43 subjects	March 21 – April 24, 2013	Pending (Preliminary VAI)
Kenneth Todd 3280 Ross Clark Circle Dothan, AL 36303	VAP.VV016 Site #75 33 subjects	April 1- 5, 2013	Pending (Preliminary NAI)

Marcus Stanbro 200 C Patewood Dr Greenville, SC 29615	VAP.VV016 Site #74 20 subjects	March 13 – 15, 2013	Pending (Preliminary VAI)
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Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Kenneth Deck, 24411 Health Center Drive, Suite 350, Laguna Hills, CA 92653

- a. What was inspected:** This inspection was conducted according to Compliance Program 7348.811. The study conducted at this site was VV015. At this site, 105 subjects were screened, 37 subjects enrolled, and 34 subjects completed the study. There was one subject who withdrew, and three subjects whose data was excluded from the primary efficacy analysis.

The field investigator reviewed the source documents for organization, completeness and legibility. She reviewed all relevant records, including informed consent documents, protocol amendments, signed investigator agreements, financial disclosure statements, IRB submissions and correspondence, Case Report Forms, adverse event reporting, inclusion and exclusion criteria, investigational study medication accountability records, monitoring logs, concomitant drugs, and sponsor audit activities. She also reviewed laboratory results and clinical investigator observations.

The FDA field investigator reviewed 19 subject records during the inspection and the primary efficacy endpoint data for all subjects. Because the e-diary information was transmitted directly to vendor (b) (4) by the subject, or via analog by the site when the subject's wireless connection did not work (see explanation below), the site did not maintain any of the e-diary information, including the primary efficacy endpoint data (Week 8, Visit 5), or any VVSymQ scores at any time points other than at baseline. During the inspection, the sponsor offered to put all data onto a CD so the investigator could review it, but this proved too difficult and voluminous. A plan was worked out whereby the FDA field investigator had read-only access to the e-diary vendor website. (b) (4) also agreed to send all Week 8 data in an Excel spreadsheet for each subject, so the FDA field investigator could corroborate the Week 8 data with the data listings, and periodically compare the data from the spreadsheet to the website to corroborate that data.

- b. General observations/commentary:** In general, records at the site were complete and accurate. The clinical investigator appeared to have adequate oversight of the study. All subjects signed informed consent appropriately, and signed the informed consent document before initiating any study-related

activities. The site reported having a lot of difficulty with the e-diaries, and wireless transmission of data. Specifically, subjects with little or no AT&T cellular reception in their homes could not transmit data from their devices nightly, and had to wait to come in for a study visit to have the data and information transmitted. As a result, the study coordinators had difficulty verifying the transmission of e-diary data contemporaneously.

The FDA field investigator compared the Independent Photography Review varicose vein assessment (IPR-V³) scores recorded by Dr. Deck at baseline and the Patient Assessment of visible varicose vein appearance (PA-V³) scores for 19 of 37 subjects, and found no discrepancies. The PA-V³ score was captured onto CRFs by the study subject and initialed and dated.

The FDA field investigator reported that all subjects met inclusion and exclusion criteria, and that Dr. Deck followed the protocol with respect to required procedures and evaluations. The FDA field investigator observed that three of 19 subjects had incorrect Varicose Vein Symptoms Questionnaire (VVSymQ) scores entered into IVRS during randomization. For example, Subject 39-1023 had a baseline VVSymQ score of 13.71, that should have been entered as 14, but instead was entered as 13. Subject 39-1053 had a VVSymQ score at baseline of 7.29, and this was entered into the IVRS as 8, whereas it should have been 7. These were reported as protocol deviations late and thus, were not reflected in the data listings provided with the assignment. No other deficiencies were noted. A Form FDA 483 was issued for this observation as failure to maintain accurate records.

The FDA field investigator noted that many protocol deviations were reported to the sponsor after the data was submitted to FDA, and thus were not included in the data listings provided with the assignment. This occurred because the study was ongoing at the time of submission of study data to the FDA, the site had not been closed out at the time of the inspection, and protocol deviations that occurred after original data submission had not been captured in the datasets provided to the FDA field investigator. The field investigator collected copies of 20 additional protocol deviation forms that had not been submitted to the FDA. For the most part, these included deviations such as out-of-window visits, or procedures not done.

The FDA field investigator verified the following data, in response to the review division's questions:

Description of protocol violations from line listings sent to the FDA field investigator:

- Baseline procedures not done within 60 days prior to treatment day (Subjects 391002, 391008, 391015, and 391070) – These were not considered protocol violations by the FDA investigator because she was able to verify that all baseline procedures took place within 60 days of treatment. No deficiencies were noted in this area.
- Patients completing the study but missing Visit 5 data (Subjects 391002, 391006, 391023, and 391047). The FDA field investigator reported that several subjects had a malfunctioning device, and were unable to transmit data wirelessly due to lack of a

signal. For this reason, the website would show missing data until the subject came into the site and the e-diaries were plugged into the analog line. Some subjects forgot to fill out the e-diary during the visit window.

- Questionnaire data missing from e-diary (Subjects 391029, 391078, 391085, and 391098). See explanation above.
- Screening procedure done prior to obtaining informed consent (Subject 391008). The FDA field investigator reviewed study records for this subject, and did not observe any screening procedures performed prior to the ICD being signed on May 14, 2011.
- IVRS and E-Diary VVSymQ Score not matching (Subjects 391015 and 391047). The FDA field investigator found this true for Subject 391047, and noted this in the Form FDA-483.
- Out of window visits (Subjects 391047, 391067, and 391085). These subjects were seen outside their windows due to their schedules. The FDA field investigator verified that for Subject 391047 the Visit 4 was early by 4 days; for Subject 391067, Visit 4 was early by 3 days; and for Subject 391085 the Visit 5 (Week 8) was out of window by 2 days. The site made appropriate attempts to bring subjects in during their scheduled windows. Subject 391061 signed the HIPAA form but failed to sign page 16 of the ICD. This subject later withdrew consent, so a signature was never obtained on the ICD. All other subjects signed informed consent appropriately.

Subjects whose data was excluded from the primary efficacy analysis (391002, 391045, and 391047)

- Subject 391002 had e-diary entries for Visit 5 (Week 8) that started on Day 79. The window for this visit was days 46 to 56.
- Subject 391045 discontinued from the study prior to Visit 5 (Week 8)
- Subject 391047 did not have enough data in the window to calculate the score for Week 8. There was only one Evening Report for this subject.

- c. **Assessment of Data Integrity:** Minor deficiencies were found during the FDA inspection at this site. These were included in the Form FDA 483, and are unlikely to affect data integrity. The study appears to have been conducted adequately at this site, and the data generated by this site appear acceptable in support of this NDA.

2. Ariel Soffer, 17901 NW 5th Street, Suite 204, Pembroke Pines, FL 33029

- a. **What was inspected:** This inspection was conducted according to Compliance Program 7348.811. The study conducted at this site was VV015. At this site, 47 subjects were screened, 35 subjects enrolled, and 34 subjects completed the study. There was one subject who withdrew, and two subjects whose data was excluded from the primary efficacy analysis by the sponsor.

An audit of 47 subjects' records was conducted. The site did not have access to the primary efficacy data, and a CD was sent from the sponsor to the site during the FDA inspection. The FDA field investigator reported that the e-dairy data was handled by the

vendor (b) (4) and although the site did not have access to this data during the study, a CD containing e-diary data was sent from the sponsor to the site for use during the FDA inspection. .

The field investigator reviewed the source documents for organization, completeness, and legibility. The inspection included the review of all relevant records, consisting of informed consent documents, protocol amendments, signed investigator agreements, financial disclosure statements, IRB submissions and correspondence, Case Report Forms, adverse event reporting, clinical source data against the data listings provided with the assignment, investigational study medication accountability, monitoring logs, concomitant drugs, and sponsor audit activities. He also reviewed laboratory results and clinical investigator observations.

- b. General observations/commentary:** The review disclosed no significant deficiencies with reporting of adverse events and transcription of source information into Case Report Forms. All subjects were evaluated to assure they met inclusion and exclusion criteria. Exceptions were granted waivers, and documentation of these waivers were kept in the subject's files. There were no significant deviations between source documents and data entered into the Case Report Forms. No significant regulatory violations were noted, and no form FDA 483, Inspectional Observations was issued.

The FDA field investigator verified the following data, in response to the review division's questions:

Subjects with protocol violations:

- Subject 1008 – had EVLT (endovenous vein laser treatment) on the non-treatment leg prior to Visit 5
- Subject 1013 – e-diary non-compliance and Visit 5 out of window
- Subject 1020 – Visit 5 out of window
- Subject 1023 – e-diary non-compliance
- Subject 1029 – e-diary non-compliance

Subjects who discontinued early:

- Subject 1045 withdrew early from study – subject left the e-diary at the office with no reason given for the withdrawal.

Subjects whose data was excluded from efficacy analysis:

- Subject 1045 was excluded because he did not complete up to Visit 5.
- Subject 1023 was excluded because of e-diary complications.

- c. Assessment of Data Integrity:** No Form FDA 483 was issued at this site. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of this NDA.

3. Brian Ferris, 12333 NE 130th Lane, Suite 425, Kirkland, WA 98034

- a. What was inspected:** This inspection was conducted according to Compliance Program 7348.811. The study conducted at this site was VV015. At this site, 88 subjects were screened, 43 subjects enrolled, and 43 subjects completed the study. There were no subjects who discontinued early from the study, and two subjects whose data was excluded from the primary efficacy analysis.

An audit of 23 subjects' records was conducted. The site did not have access to the primary (Week 8, Visit 5) efficacy data, although a CD was sent from the sponsor to the site during the FDA inspection. The FDA field investigator reported that the e-diary data was handled by the vendor (b) (4) and the site did not have access to this data during the study.

The field investigator reviewed the source documents and records for 23 subjects at this site. The inspection included the review of IRB, monitor and sponsor correspondence, Informed Consent Documents for all subjects, drug accountability records, primary and secondary efficacy endpoints (after data was provided by the sponsor), protocol deviations, adverse events, and clinical investigator oversight of the study.

- b. General observations/commentary:** The review disclosed no significant deficiencies with reporting of adverse events and transcription of source information into Case Report Forms. The FDA field investigator reported that the site only had e-diary data for the screening visit, and that the remaining data was downloaded from the diary into modems at the site, and the data was transmitted directly to the sponsor via a fax line. Dr. Ferris and the study coordinator confirmed that they never received any CDs or other electronic data from the diaries from the sponsor. The FDA field investigator spoke with the sponsor and (b) (4) during the inspection. The sponsor sent an Excel spreadsheet (PDF format) with the endpoint data, and the FDA field investigator set up an account to review e-diary data online.

All subjects were properly consented. Drug accountability was adequately documented. The review of primary and secondary efficacy data points showed no discrepancies with the data listings. The site reported all protocol deviations. The site documented all adverse events and there were no discrepancies with the adverse events included on the data listings. No serious adverse events occurred at this site.

A FDA Form 483, Inspectional Observations was issued to Dr. Ferris for not conducting an investigation in accordance with the investigational plan. Specifically: 1) Six subjects were issued e-diaries before review of inclusion/exclusion criteria review was completed; 2) one subject was treated with investigational drug before review of inclusion/exclusion criteria was completed; the FDA field investigator reported that all protocol deviations were appropriately reported to the sponsor and IRB.

In addition, three items were discussed at the close of the inspection: 1) Ensuring record keeping is complete (missed initialing by subject on questionnaire); 2) ensuring complete record retention (missing pages in subject binders, however, study coordinator was able to retrieve them); 3) show more documentation of PI study oversight. For example, since the PI stated that most correspondence with the sponsor was via telephone, he was advised that he should document phone calls, emails, etc. that showed the PI's involvement with the Sponsor or major decisions in study conduct.

- c. **Assessment of Data Integrity:** Three items noted above were contained on the Form FDA 483 issued at this site. The items, listed above, are unlikely to affect data integrity. The study appears to have been conducted adequately and the data generated by this site appear acceptable in support of this NDA.

Note: Observations noted for this site are based on preliminary communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

4. **Kenneth Todd, 3280 Ross Clark Circle, Dothan, AL 36303**

- a. **What was inspected:** This inspection was conducted according to Compliance Program 7348.811. The study conducted at this site was VV016. At this site, 58 subjects were screened, 33 subjects enrolled, and 32 subjects completed the study. There was one subject who discontinued early from the study, and one subject whose data was excluded from the primary efficacy analysis by the sponsor. No serious adverse events occurred at this site during the study.

The FDA field investigator reviewed 33 subject records for proper informed consent procedures, inclusion and exclusion criteria, primary efficacy endpoint (ensuring consistency between VVSymQ questionnaire CRF and source documents at screening and Visit 5 (Week 8)), secondary efficacy endpoints (IPR-V³ and PA-V³) at screening, and subject records at baseline (Visit 2), Visit 4 (Week 4) and Visit 5 (Week 8). The FDA field investigator reviewed 15 subject records for progress notes, inclusion and exclusion criteria, physical exams, protocol violations, adverse event reports, and concomitant medications.

The FDA field investigator reported that the site did not have access to the primary efficacy data (e-diary data) after baseline. After baseline, the site was responsible for downloading and transmitting e-diary information to (b) (4) monitoring the subject's compliance with e-diary entries, and collecting the e-diary equipment from the subject at the end of the study. During the inspection, (b) (4) and the sponsor provided the FDA field investigator with a CD that contained the e-diary VVSymQ scores at Visit 2 (Baseline), Visit 4 (Week 4) and Visit 5 (Week 8).

- b. General observations/commentary:** Overall, site records appeared to be complete, legible, and organized. No underreporting of adverse events was noted during the inspection. A review of subject source records and CRF documents and a comparison of information in the data listings of VVSymQ scores at baseline for 33 subjects revealed a difference of ± 1 point for five subjects. The [REDACTED] (b) (4) showed current VVSymQ baseline scores for the five subjects to match the data listings. The FDA field investigator reported that for Subject 1029, a 4-day average (instead of a 7-day average) had been used to calculate the VVSymQ score at Visit 5 (Week 8).

Minor issues were noted including: 1) not obtaining informed consent from some subjects when a revised informed consent document became available; 2) not completing the exclusion criteria section of the case report form for six subjects (1009, 1012, 1017, 1027, 1043 and 1048); 3) no documentation that discontinued Subject 1049 was informed of the consequences of withdrawing early from the study; 4) failure to document temperature for two of fifteen received shipments of study drug; 5) not completing screening source documents for VVSymQ score for determining eligibility for three subjects (1003, 1029 and 1031). These subjects were eligible. The above observations are unlikely to affect the overall integrity of the data at this site. No violations were cited and no Form FDA 483 was issued.

Review of records was conducted for nine reported protocol violations, as per the assignment. These were as follows: e-diary compliance for Subjects #1009, 1010, 1039, 1056 and 1058; missing ultrasound data for Subjects #1005 and 1049; and missed study drug administration for Subject #1058. Review of protocol violations for Subject #1049 revealed that the patient received treatment at Visit 2 on April 6, 2011 and failed to return for Visit 3 on April 11, 2011 for an ultrasound. The subject called the site on April 12, 2011 requesting to be withdrawn from the study, stating that she did not have time to participate.

Review of site monitor reports revealed 3 missed labs for Subject #1002, 1003, 1004, 1005, 1007 and 0139, and an out-of-window visit for Subject #1017. These findings are unlikely to significantly affect the efficacy or safety data at this site. Review of records for Subjects #1003 and 1005 revealed protocol deviations that documented the site had been unable to ship lab samples drawn at Visit 3 due to a FedEx holiday.

- c. Assessment of Data Integrity:** No FDA 483 was issued at this site. The study appears to have been conducted adequately and the data generated by this site appear acceptable in support of this NDA.

Note: Observations noted for this site are based on preliminary communications with the FDA investigator and review of a preliminary EIR. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

5. Marcus Stanbro, 200 C Patewood Drive, Suite 300, Greenville, SC 29615

- a. What was inspected:** This inspection was conducted according to Compliance Program 7348.811. The study conducted at this site was VV016. At this site, 27 subjects were screened, 20 subjects enrolled, and 19 subjects completed the study. There was one subject (1019) who discontinued early from the study and one subject (1019) whose data was excluded by the sponsor from the primary efficacy analysis.

The FDA field investigator reviewed all subject records for the primary efficacy endpoint (VVSymQ score) at baseline, and compared with the data listings. The data at the Visit 5 (8 week visit) was not available at the site during the inspection. The FDA field investigator reviewed the informed consent process for all subjects, the protocol violations, adverse events, inclusion and exclusion criteria, and drug accountability records. She compared the source documentation to the data in the Case Report Forms. The site did not have possession of the e-diary data, during the inspection.

- b. General observations/commentary:** No discrepancies were noted in comparing the source documents and the data listings for the VVSymQ score at baseline. No significant issues were found in the consent process, although a few subjects did not initial one or two pages of the 15-page consent form. The source documentation supported the data in the case report forms, although there were a few minor transcription errors. All subjects met the inclusion and exclusion criteria. No deficiencies were noted in the drug accountability records.

A Form FDA 483 was issued at the conclusion of the inspection with two observations. The first observation was that an investigation was not conducted according to the investigational plan. Specifically, review of source documents and case report forms for 20 subjects revealed that all subjects were provided with an e-diary prior to completion of all screening procedures. For example, Subject 1002 received an e-diary on February 18, 2011, although the physical examination, duplex ultrasound, and blood samples were not completed until March 4, 2011. Subject 1027 received an e-diary on May 9, 2011, although the physical examination and duplex ultrasound were not conducted until May 20, 2011. The FDA field investigator reported these had been reported as protocol violations to the sponsor.

The second observation was that, for 6 of 20 subjects (1002, 1003, 1004, 1006, 1007, 1008), the clinical site entered the screening VVSymQ score into the IVRS at randomization instead of the baseline VVSymQ score (baseline VVSymQ score was required by the protocol). For example, Subject 1002 had a screening VVSymQ score of 20 and a baseline VVSymQ score of 10, and Subject 1005 had a screening VVSymQ score of 15 and a baseline VVSymQ score of 5.57. All six subjects were randomized on March 4, 2011, entering

their screening VVSymQ score into IVRS. The study site submitted a protocol deviation concerning this incident, received clarification, and all subjects randomized after March 4, 2011 used the correct VVSymQ score. Because the protocol required a screening VVSymQ score of ≥ 7 points for inclusion, these subjects appear to meet the eligibility criteria. However, these scores may affect the primary efficacy endpoint which was calculated using the absolute change from baseline in the 7-day average e-diary VVSymQ score at Week 8. It is deferred to the Review Division to determine if this finding is significant or likely to impact the primary efficacy analysis.

The FDA field investigator verified the following data, in response to the review division's questions:

1. It was not possible to verify the VVSymQ score at Week 8, as this information was entered by the subject into the e-diary which was transmitted to the sponsor. The site did not collect or have access to this data during the inspection.
 2. As per the assignment, Dr. Stanbro's site had 25 reported protocol violations. A summary of these protocol violations is as follows:
 - Five were related to study visits outside of treatment windows
 - Six were related to use of screening VVSymQ scores instead of baseline VVSymQ scores at randomization
 - 25 protocol violations related to e-diaries which were given to subjects prior to completion of screening procedures
 - Three protocol violations for subjects failure to initial or date each page of the ICD
 - Two protocol violations for subjects receiving alternative treatments to study leg without notifying staff.
 3. Subject 1019 was discontinued from the study for failing to keep the scheduled appointments. This subject's data was excluded from the primary efficacy analysis.
- c. **Assessment of data integrity:** A one observational FDA 483 was issued at this site. In general, the data appear acceptable, although the Review should assess the impact of the six subjects who were reported to use screening VVSymQ scores in the calculation of the primary efficacy endpoint.

Note: Observations noted for this site are based on the Form FDA 483 and preliminary communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Five clinical investigator sites (all domestic) were inspected in support of NDA 205098. No regulatory violations were found during the inspections at two clinical investigator sites: Site #37 (Ariel Soffer, FL) and Site #75 (Kenneth Todd, AL), and no Form FDA- 483 was issued.

Minor regulatory violations were found during the inspections at Site #39 (Kenneth Deck, CA) and Site #33 (Brian Ferris, WA) and a one observational Form FDA 483 was issued for failure to follow the investigational plan (Deck site), and inaccurate records (Ferris site). A one observational FDA 483 was issued at Site #74 (Stanbro, SC), and OSI defers to the review division to determine the significance of using screening VVSymQ scores instead of the baseline score for calculation of the primary efficacy endpoint in six subjects as described above.

Although regulatory violations were noted as described above, they are unlikely to significantly impact the primary efficacy or safety analysis for this study. Therefore, the data from this study may be considered reliable based on available information.

Note: The final EIRs for Site #33 (Brian Ferris, WA), Site #75 (Kenneth Todd, AL) and Site #74 (Marcus Stanbro, SC) were not available at the time this CIS was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIRs.

{See appended electronic signature page}

Sharon K. Gershon, Pharm.D.
Reviewer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

{See appended electronic signature page}

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

/s/

SHARON K GERSHON
06/28/2013

SUSAN LEIBENHAUT
06/28/2013

SUSAN D THOMPSON
06/28/2013

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	AT 2013-022
APPLICATION NUMBER	NDA 205098
LETTER DATE/SUBMISSION NUMBER	001
PDUFA GOAL DATE	December 4, 2013
DATE OF CONSULT REQUEST	February 7, 2013
REVIEW DIVISION	Division of Cardiovascular and Renal Products (DCRP)
MEDICAL REVIEWER	Khin U
REVIEW DIVISION PM	Michael Monteleone
SEALD REVIEWER(S)	Jessica Voqui
REVIEW COMPLETION DATE	June 7, 2013
ESTABLISHED NAME	Polidacanol endovenous microfoam (PEM)
TRADE NAME	Varithena (under review)
APPLICANT	Provensis Ltd (BTG International Ltd)
ENDPOINT(S) CONCEPT(S)	Symptoms associated with superficial venous incompetence (i.e., varicose veins)
MEASURE(S)	Varicose Veins Symptoms Questionnaire (VVSymQ)
CLINICAL OUTCOME ASSESSMENT TYPE	PRO
INDICATION	Treatment of incompetent great saphenous veins (GSV), accessory saphenous veins and visible varicosities of the GSV above and below the knee and improvement of the symptoms of superficial venous incompetence and the appearance of visible varicosities in the GSV system.
INTENDED POPULATION(S)	Adults (18-75 years of age) with superficial venous disease manifested by either symptoms or visible varicosities, with saphenofemoral junction (SFJ) incompetence due to reflux in either the great saphenous vein (GSV) or major accessory veins.

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A. EXECUTIVE SUMMARY

This Study Endpoints and Labeling Development (SEALD) review is provided as a response to a request for consultation by the Division of Cardiovascular and Renal Products (DCRP) regarding NDA 205098. The sponsor used the Varicose Veins Symptoms Questionnaire (VVSymQ) in two pivotal phase 3 trials for the measurement of varicose veins symptoms for a primary endpoint measure in adult patients with superficial venous disease manifested by either symptoms or visible varicosities. The Division requested that SEALD review the validation methods and results, clinical significance of the changes in VVSymQ scores as related to the Patient Global Impression of Change (PGIC) with respect to symptoms.

Previous reviews of the VVSymQ in the earlier stages of instrument development revealed concerns regarding the content validity of the instrument. Some key concerns were in regards to the item reduction from the 9 core symptoms to 5 symptoms, lack of diverse demographics in the qualitative research, and whether it was more appropriate to assess symptoms using duration/frequency or severity. All of these issues have been adequately addressed. Supplementary symptoms were included in the electronic diary (eDiary), as well as items to assess symptom severity. The 5-item VVSymQ score (duration) was compared to score configurations that used 7- and 9-item scores (intensity and duration sets of items were compared). The 5-item summary score demonstrated high correlation with the other score configurations in terms of Baseline score and changes, indicating that the shorter instrument may be acceptable. In regards to the demographics of the study population in the qualitative studies, these were comparable to the demographics of the patients who enrolled in the phase 3 clinical trials. Additionally, the psychometric properties of the instrument appear to be adequate in regards to reliability, construct validity, and ability to detect change.

In the primary efficacy results from the two pivotal phase 3 trials, the VVSymQ detected a substantial treatment effect that was also supported by multiple responder analyses. However, there was an unexpected result in Study 016 for PEM 1.0% that did not demonstrate a typical dose-response effect compared to the lower doses of 0.125% and 0.5%, both of which had a greater proportion of responders and were statistically significant. It is likely that this result was due to the study design of Study 016, which allowed a second treatment. Overall, the results of the responder analyses appear to be reasonable and support that patients experienced a clinically meaningful change in symptoms as a result of using the treatment.

The review concludes that the evidence submitted by the sponsor has addressed previous concerns about the instrument and is adequate to demonstrate that the VVSymQ measures symptoms of superficial venous disease in the stated context of use.

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B. STUDY ENDPOINT REVIEW

The VVSymQ is a modification of an instrument, the VEINES-QOL/Sym (Lamping et al. 2003) that was developed as part of the Venous Insufficiency Epidemiology Study (VEINES). Based on discussions with the Agency during the Special Protocol Assessment process, the sponsor further refined the VEINES-QOL/Sym based on additional qualitative and quantitative research and advice provided by the Agency (see previous SEALD reviews for IND 63420: Trentacosti 06/17/09, Miskala 01/13/10, and Miskala 06/25/10). The most recent SEALD review (Miskala 06/25/10), concluded that the sponsor's qualitative research submitted at that point was sufficient to establish that the initial pool of nine symptoms (heaviness, aching, swelling, night cramps, heat or burning sensation, restless legs, throbbing, itching, tingling sensation) are of relevance to patients in the clinical trial population; however, further work would be needed to support item reduction.

1 CLINICAL OUTCOME ASSESSMENT MEASURE(S)

Varicose Veins Symptoms Questionnaire (VVSymQ) – Appendix A

The VVSymQ is a 5-item instrument that includes the following symptoms:

- Heaviness
- Achiness
- Swelling
- Throbbing
- Itching

Patients are asked to complete each item thinking about their day using a duration-based response scale (i.e., how much time each day they experience each symptom). The response options are as follows: “None of the time”, “A little of the time”, “Some of the time”, “A good bit of the time”, “Most of the time”, and “All of the time”. The items are framed to limit the recall period “since waking up today”, and to focus on the leg to be treated.

Prior versions: The initial version of the VVSymQ contained the same 5 items and response options, but utilized a 1-week recall period and was administered using a paper questionnaire.

Timing, method, mode of administration: In the phase 3 pivotal clinical trials (Study 015 and Study 016), the VVSymQ was administered daily using a handheld electronic diary device (e-Diary) in the context of an expanded daily diary that contains additional symptoms, an evaluation of activity level, and evaluation of symptom intensity. The additional symptoms include: heat or burning sensation, tingling sensation, night cramps, and restless legs.

Prior to designated time points during the clinical trial, patients used the e-Diary for a 10 day period, completing the assessment between 6:00p and 11:45p. These periods were immediately

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before the following efficacy assessment time points: Visit 2/Baseline, Visit 4/Week 4, and Visit 5/Week 8 (where “Week” refers to the week post-treatment). There was also an assessment period for Visit 10/1 Year.

Training methods and materials:

Subject: Subjects were trained by the investigative site during an interactive one-on-one session using a training feature on the e-diary device, which generally required less than 30 minutes. A quick reference guide was provided to patients to take home. Additionally, a 24-hour help desk was available to patients and investigative sites for technical support.

Site and investigator training: The investigative site staff was trained by the provider of the e-Diary at the investigator meeting, or on-site by the study monitor. This included didactic explanation of the system operation and hands-on demonstrations. The site was trained on use of the e-Diary device and the secure website that facilitated review of the patient diary data that has been transferred to the central server.

Scoring algorithm: Each of the 5 items was scored from 0 (“None of the time”) to 5 (“All of the time”) and were summed for a daily VVSymQ score that ranged from 0 (no symptom burden) to 25 (worst symptom burden).

2 TARGET PRODUCT PROFILE

The following labeling language has been proposed for the indication:

“VARITHENA (1% polidocanol injectable microfoam) is indicated for the treatment of incompetent great saphenous veins, accessory saphenous veins and visible varicosities of the great saphenous vein (GSV) system above and below the knee. VARITHENA improves the symptoms of superficial venous incompetence and the appearance of visible varicosities (b) (4)

Additionally, the VVSymQ and symptom improvement claims are described in the text with an accompanying table in the Clinical Studies section as follows:

“For both clinical trials, the primary efficacy endpoint was improvement in patient symptoms, as measured by the change from baseline to Week 8 in the 7-day average electronic daily diary VVSymQ™ score. The VVSymQ™ score is a patient-reported outcome measure based on daily patient assessment of the varicose vein symptoms determined to be most important to patients: heaviness, achiness, swelling, throbbing, and itching. VVSymQ™ scores range from 0-25, where 0 represents no symptoms and 25 represents all 5 symptoms experienced all of the time. Results are shown in Table (b) (4)

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For both Studies 1 and 2, treatment with VARITHENA 1.0% was superior to placebo in improving symptoms as measured by VVSymQ™, when either a duration or an intensity scale was used to measure patients' symptoms. (b) (4)

[Redacted]

[Redacted]

[Redacted] (b) (4)

3 ENDPOINT MODEL

Endpoint Model for Symptoms

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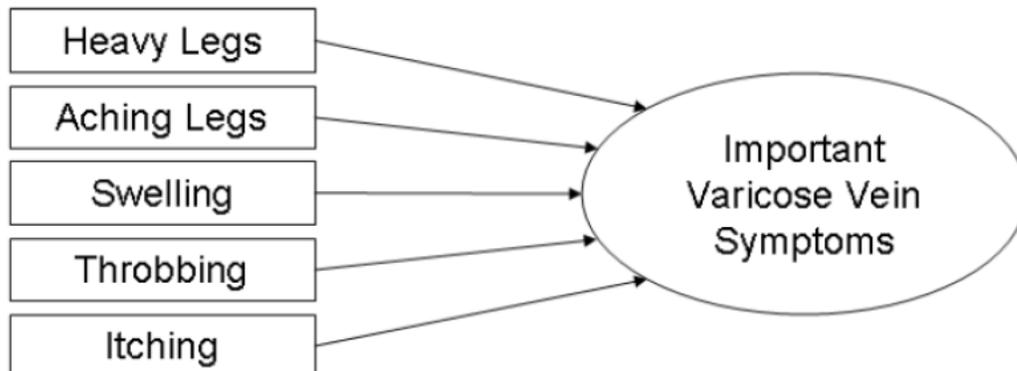
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Label Objective	Concept	Endpoint
PEM improves symptoms of superficial venous incompetence of the GSV system	Symptoms of varicose veins	Absolute change from Baseline to Week 8 post-treatment of the 7-day average VVSymQ score

This endpoint model does not describe all clinical endpoints used for the phase 3 clinical trials or the hypothesized relationships among the clinical outcome assessment (COA) endpoints in terms of the measurement concepts. The following efficacy endpoints were used in the phase 3 pivotal studies, Study 015 and 016:

- Primary endpoint: Absolute change from baseline to Week 8 in the 7-day average VVSymQ score in the pooled PEM group, versus Vehicle placebo group.
- Co-secondary endpoints:
 - IPR-V³ score: Independent Photography Review – Visible Varicose Veins appearance assessment as reviewed by an independent review panel
 - PA-V³ score: the Patient Self-assessment of Visible Varicose Veins, a patient self-assessment of varicose vein appearance
- Tertiary:
 - Duplex ultrasound response
 - VCSS
 - VEINES-QOL

4 CONCEPTUAL FRAMEWORK



The conceptual framework of the measure appears to correspond to the study endpoint concept of varicose vein symptoms measured in the clinical trial protocol (b) (4)

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5 CONTENT VALIDITY

VEINES-QOL/Sym

The original VEINES-QOL/Sym content area was based on the following (Lamping et al 2003):

- Literature review of PROs in chronic venous disorders of the leg (CVDL)
- Review of existing measures of outcome in CVDL
- Expert clinical opinion

The article by Lamping et al (2003) describes that they

“generated questionnaire items for both domains through consensus discussions with a multidisciplinary expert group of clinicians and methodologists with expertise in CVDL, questionnaire design, psychometrics, and epidemiology. The content and format of the questionnaire were modeled after the SF-36. We modified generic SF-36 questions to make them specific to CVDL and developed new CVDL-specific questions with the same format and response scales of the SF-36”.

The original instrument was developed in English.

As noted in a previous SEALD review (Miskala 01/13/10), “The original VEINES-QOL/Sym did not include direct patient input into selection and drafting of instrument items. However, the sponsor states that the instrument was tested in patients using face-to-face interviews in a small sample of patients to clarify ambiguities in wording, confirm appropriateness of response options, to determine acceptability and to assess completion time.”

VVSymQ

Initial Version of the VVSymQ (Diary Versions 1 and 2):

The sponsor modified the original VEINES-QOL/Sym instrument and utilized a subset of symptom items for the VVSymQ.

The description and details of early stages of instrument development for the VVSymQ can be found in the previous SEALD review (Miskala 01/13/10). In summary, these included:

- initial focus groups and cognitive debriefing interviews which were conducted in 2008 that included many participants who had no or few symptoms;
- additional qualitative studies were conducted with the goal to confirm instrument content in more symptomatic patients, evaluate appropriate response options and recall period, and determine importance of frequency and severity of symptoms;
 - These included three focus groups (n = 19) and semi-structured cognitive debriefing interviews (n = 10) with Versions 1 and 2 of the diary.

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Based on the results of these qualitative studies, the initial version of the VVSymQ included five items: heavy legs, aching legs, swelling, throbbing, and itching. Patients rated these on a frequency response scale ranging from “none of the time” to “all of the time” for a 7-day recall period.

Reviewer’s comments: In the previous SEALD review, there were a number of concerns regarding the recall period, possible biased results due to the symptom eligibility criteria, and the lack of demographic diversity (most subjects interviewed were non-Hispanic white women) of the participants. Additionally, it was unclear whether the 5 items that were included in the draft instrument adequately assessed pain.

Of note, the demographic diversity was similar to the population enrolled in the phase 3 trials, the majority of which comprised of non-Hispanic white females. Therefore, the study population in the qualitative studies were acceptable for the context of use in the phase 3 clinical trials.

Final Version of the VVSymQ (Diary Version 3):

The sponsor implemented the Initial Version of the VVSymQ in an observational study and a pilot Phase 3 study and submitted the Initial Version to the Agency with the goal of utilizing it in phase 3 clinical trials. Based on feedback from the Agency, the sponsor developed an electronic diary with the 9 symptoms from the modified VEINES-Sym, evaluated on both duration and intensity-based response scales, and 2 activity items. The resulting 20-item diary was called the Daily Diary for Varicose Veins Symptoms, Activity, and Inactivity Items. The VVSymQ is contained within this diary. Qualitative studies were conducted to evaluate the diary in the targeted patient population to test patient comprehension and the appropriateness of the evolving versions of the instrument.

Based on feedback from the Agency (SPA-No Agreement letter dated 01/26/10), the following changes were made to the instrument:

- addition of the following supplementary symptoms: “heat or burning sensation”, “tingling sensation”, “night cramps”, and “restless legs”;
- items were developed with the 6-point categorical response options used in previous VVSymQ versions to assess the symptoms “leg cramps” and “restless legs” using the recall period “last night” because previous qualitative interviews indicated that these symptoms typically occurred during the night.
- items were added to assess all symptoms at their “worst” severity in the past 24 hours, using an 11-point numeric rating scale (0 to 10, where 0 = *none* and 10 = *as bad as you can imagine*).

Cognitive interviews:

The final version of the VVSymQ was included in Version 3 of the diary, which was tested in two waves of cognitive interviews with five patients each (n = 10). Patients were enrolled at the

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Seattle, WA and Bellevue, WA clinics. The demographics of the participants were similar to the previous qualitative studies and were predominantly female, white and non-Hispanic, with a higher college education. The mean patient age was 57.3 years (range: 51-62 years). The majority of patients had venous disease that was characterized as CEAP Classes 3 or 4. The results of both waves indicated that patients endorsed Version 3 of the diary and had little difficulty with language or understanding and interpretation of the items or response scales. This was the final instrument that was utilized in the phase 3 trials.

6 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

Although the sponsor provided quantitative results for the Initial and Final Version of the VVSymQ, this review will focus on the Final Version that was used in the phase 3 clinical trials.

Study RS-002:

The measurement properties of the VVSymQ were evaluated in the context of treating patients with varicose veins using an unapproved foam sclerotherapy. Patients had three in-clinic visits and at each visit, the patient completed PRO instruments and the clinician completed two clinician assessments. Additionally, the patient completed an eDiary each evening for approximately 14 days between Visits 1 and 2 (where Week 1 = screening period and Week 2 = baseline period). At Visit 2, patients received treatment. Immediately prior to Visit 3 (8 weeks after treatment), patients completed the eDiary each evening for approximately 10 days (post-treatment period).

Results:

Forty-two patients were screened for the study, and 40 patients were enrolled. The patient sample was representative of a typical varicose vein population, with more females seeking treatment (62.5%), and patients reporting at least moderately severe varicose vein symptom according to the VCSS.

Item reduction: Alternative Baseline symptom scores were computed using 7 and 9 duration-based symptoms, as well as 5, 7, and 9 intensity-based symptoms and correlated with the VVSymQ score. These correlations were very high, ranging from 0.9105 to 0.9802, suggesting that they are measuring the same underlying construct. The 5-item VVSymQ score likely reflects a similar construct as the other score configurations and may be used a summary score.

Additionally, the correlations of change between Baseline and Post-Treatment (Week 8), between the VVSymQ and other score configurations was high, ranging from 0.8862 and 0.9790.

Reviewer's comments: Clinical expert input was not used for the item reduction as previously suggested to the sponsor. However, this method is still supportive of the 5-item scoring.

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Endorsement of items: All of the VVSymQ symptoms were endorsed by at least 75% of patients during the Baseline period. The average individual Baseline symptom scores ranged from 1.5 to 2 (on a 0 to 5 scale) indicating that symptoms were experienced “a little of the time” to “some of the time” each day. At the end of the 8-week post-treatment period, patients mean levels on individual symptoms reduced to 0.5 or below (i.e., “a little of the time” to “none of the time”).

Test-retest reliability (from Screening to Baseline): The intraclass correlation coefficient (ICC) was 0.96, indicating high test-retest reliability.

Internal consistency: Cronbach’s alpha values for correlations between the 7-day average VVSymQ 5-item score and the other configurations of the diary score (7 items or 9 items) were > 0.7 , indicating good scale consistency.

Construct validity: The construct validity was evaluated by correlating the VVSymQ and other instruments such as the VEINES-QOL/Sym, CIVIQ-20, CEAP, and VCSS.

- **Modified VEINES-QOL/Sym**: As expected, the VVSymQ scores had a high correlation ($r = -0.7268, -0.7548, \text{ and } -0.6702$) at Baseline, Week 8, and change from Baseline to Week 8, respectively. The negative correlations occurred because higher scores are more favorable for the the modified VEINES-QOL/Sym scores.
- **CIVIQ-20**: The Chronic Venous Disease Symptoms Questionnaire (CIVIQ) has 20 items related to the patient’s symptoms, actions and activities, and feelings over the past four weeks. Items are rated on a five-point scale that ranges from 0 (no trouble, minimal problem) to 5 (greatest intensity or trouble). There was a significant but modest correlation with the VVSymQ scores ($r = 0.5175, 0.5868, \text{ and } 0.4847$) at Baseline, Week 8, and change from Baseline to Week 8, respectively. The Pain and Psychological CIVIQ-20 subscales showed the strongest relationship to the symptoms.
- **Clinician-reported outcomes**: The VVSymQ was compared to clinician-reported measures of vein disease severity, the CEAP and the VCSS. The CEAP (Clinical, Etiology, Anatomy, and Pathophysiology) classification of the American College of Phlebology is used to characterize the form and severity of venous disease using seven grades of severity. The Venous Clinical Severity Score (VCSS) is a clinician-rated instrument that rates signs and symptoms of varicose veins on a four-point scale (e.g., none, mild, moderate, severe).

The results showed no correlation between the VVSymQ and the CEAP ($r = -0.05$), and a very low correlation with the VCSS ($r = 0.14$). There was not a clear relationship between the clinician-reported outcomes and the VVSymQ scores.

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Reviewer's comments: The lack of correlation between the VVSymQ, a patient-reported outcome, and the clinician reported outcomes is not completely unexpected. These instruments are measuring different concepts in two ways: the reporter is looking at different characteristics of the symptoms, and each type of reporter is looking at these characteristics from a different perspective (either as a clinician or a patient).

- PA-V³: The PA-V³ was designed to evaluate the patient's perspective on the appearance of their varicose veins. The correlations between the 7-day average VVSymQ score and the appearance score were $r = 0.318$ and $r = 0.304$ at Baseline and at Week 8. The correlation is modest but significant and suggests that there may be a relationship between appearance and symptoms.
- IPR-V³: The IPR-V³ is an assessment of improvement in appearance, as assessed by a clinician. Changes in the IPR-V³ correlated with changes in VVSymQ score ($r = 0.176$, $p = 0.0002$) and individual symptom scores, with the exception of itching, ($r = 0.101-0.343$, $p = <0.0001$ to 0.005). Results from Study 015 are reported here, but there were similar results with Study 016.
- Duplex Ultrasound Response: The Duplex Ultrasound is used to assess the improvement in vascular hemodynamics and improvement in GSV incompetence. Changes in the VVSymQ score and the Duplex Ultrasound Response had small but statistically significant correlations ($r = -0.193$ [Study 015] and -0.228 [Study 016], $p < 0.0001$ [both studies]).

Ability to detect change: Large reductions were detected on the VVSymQ between Baseline and Week 8. The effect size (i.e., change in mean value from Baseline to Week 8, expressed as a proportion of the standard deviation of the baseline pre-treatment scores) was 1.6. A large effect size is typically 0.8 or greater.

Reviewer's comments: It is generally recommended that the ability to detect change is assessed by comparing the change in the PRO instrument scores to change in other similar measures that indicate the patient's state has changed with respect to the concept of interest. However, the results from the blinded, placebo controlled phase 3 trials showed a large treatment effect. Therefore, there is not a notable concern about the ability to detect change.

7 INTERPRETATION OF SCORES

An anchor-based approach was used to define a responder with a patient global impression of change (PGIC). The PGIC was administered to patients at various time points, and the results of Week 8 were used to support the responder definition.

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Patient Global Impression of Change in Symptoms

Please rate the change in your varicose vein symptoms today compared to your varicose vein symptoms before you received treatment at the start of the study.

<i>Much improved</i>	+3
<i>Moderately improved</i>	+2
<i>A little improved</i>	+1
<i>No change</i>	0
<i>A little worse</i>	-1
<i>Moderately worse</i>	-2
<i>Much worse</i>	-3

The threshold for clinically meaningful change is “moderately improved”. Of the 40 patients in Study RS-002, most patients reported that their symptoms were “much improved” (87.5%), some reported “moderately improved” (10%), and one reported that their symptoms were “a little improved”. No patient reported “no change” or worsening. Patients who reported that their symptoms were moderately or much improved had mean improvements of 6.3 points on the VVSymQ. Since there were no patients that reported an unchanged or worsening status, there were too few patients at the lower end of the scale to determine a precise estimate. The mean change in the 7-day average VVSymQ score of -6.3 for the patients with improvement on the PGIC can be used as an upper bound. The results of the cumulative distribution function for the VVSymQ showed that 50% of patients had an improvement of at least -5.8 points. Therefore, the RS-002 results show that a change from Baseline to Post-Treatment of approximately -6 reflects a clinically meaningful change. Additionally, the larger phase 3 trials (Study 015 and Study 016) determined an anchor-based threshold of -4.66 and -4.59, respectively.

8 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

The sponsor states that language translation and cultural adaptation was not performed for the VVSymQ.

9 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

Initial versions of the VVSymQ were administered in a paper and pencil format and the final instrument was administered in an e-Diary as described in Section B.1. of this consult review.

10 ANALYSIS AND RESULTS

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In summary, there were two randomized, blinded, placebo-vehicle controlled, phase 3 pivotal studies that utilized the VVSymQ for the primary endpoint, Study 015 and 016. Both of these trials had the same study design, which compared a vehicle placebo to several dose concentrations of PEM (0.125% or control, 0.5%, 1.0%, and 2.0% concentrations in Study 015, and all but the 2.0% dose in Study 016). The primary efficacy analysis was conducted at Week 8 post-treatment, comparing against Baseline values pooled PEM 0.5% and 1.0% concentrations in Study 016 and PEM 0.5%, 1.0%, and 2.0% concentrations in Study 015.

Key inclusion criteria:

- Adult patients (18-75 years of age)
- SFJ incompetence associated with incompetence of GSV or other major accessory vein and superficial venous disease manifested by both symptoms and varicosities, where SFG incompetence was the predominant source of reflux
- VVSymQ score ≥ 7 points at screening
- PA-V³ score of moderately noticeable, very noticeable, or extremely noticeable in leg to be treated
- IPR-V³ score of moderate, severe, or very severe in leg to be treated

Primary efficacy analyses: The primary efficacy endpoint was the absolute change from baseline in the 7-day average eDiary VVSymQ score at Week 8 in patients treated with PEM 0.5%, 1.0%, and 2.0% (pooled), compared with vehicle, using LOCF. Other endpoints are described in Section B.3. of this consult review. The last 7 calendar days of the 10-day e-diary collection period were to be used in calculation of the VVSymQ score. Complete data (i.e., all 5 VVSymQ diary symptom items) were required for at least 4 of the 7 calendar days immediately before the scheduled study visit; if these data were not available, the VVSymQ score was not to be calculated for that time point. This endpoint was to be evaluated using analysis of covariance (ANCOVA) with treatment group and site as class variables and the corresponding baseline score from the questionnaire as a continuous covariate. Pooled comparisons of the pooled PEM dose groups to Vehicle were to be conducted using a model that used the data from all treatment groups and ninety-five percent confidence intervals (CIs) were to be constructed about the estimated treatment difference based on the model estimates and associated variability.

In the individual Studies 015 and 016, across endpoints, each comparison of pooled PEM (excluding 0.125% PEM) versus vehicle placebo was conducted at the $\alpha = 0.05$ level (two-sided) with study-wise Type I error controlled using a hierarchical approach as described in the following figure.

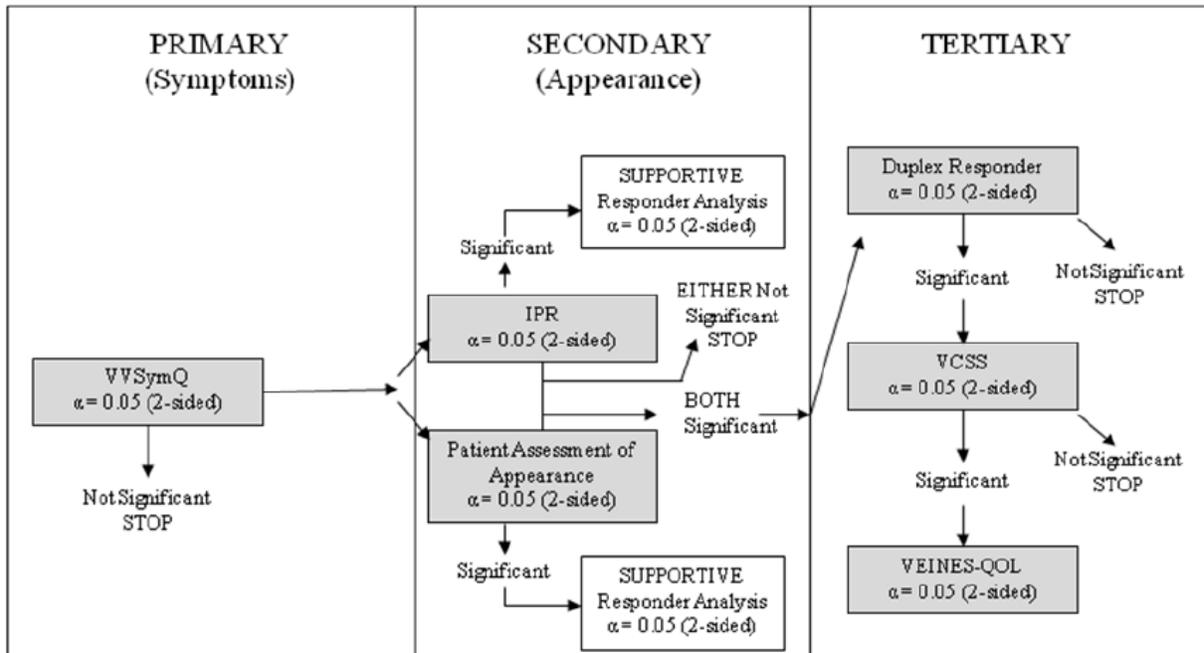
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Figure 1: Hierarchical Approach to the Efficacy Endpoint Comparisons, Studies 015 and 016



Results:

In Study 015, the treatment groups with PEM 0.5%, 1.0%, and 2.0% (pooled) demonstrated a greater improvement in the VVSymQ score compared with vehicle placebo (-5.44 versus -2.13 points, respectively). This difference was statistically significant. In Study 016, the treatment groups with PEM 0.5% and 1.0% (pooled) demonstrated a greater improvement in the VVSymQ score compared with vehicle placebo (-5.53 versus -2.00 points). This difference was statistically significant. In both studies, the unpooled data in the different dose groups also demonstrated a statistically significant difference.

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Table 7: Primary Efficacy Analysis: Absolute Change from Baseline to Week 8 in VVSymQ Score (LOCF), Efficacy Populations of Studies 015 and 016

Parameter : Study Treatment Group	N ^a	Baseline ^b		Adjusted Mean ^c Change from Baseline		Comparison vs. Placebo	
		Mean	SE	Adjusted Mean	SE	Estimate (95% CI) ^d	P-value ^e
VVSymQ: Study 015							
Placebo	55	8.60	0.687	-2.13	0.452		
PEM 0.125% (control)	56	9.01	0.650	-4.63	0.447	-2.49 (-3.72, -1.27)	0.0001
PEM 0.5%	51	9.30	0.615	-5.68	0.483	-3.54 (-4.80, -2.29)	<0.0001
PEM 1.0%	50	8.82	0.663	-4.87	0.477	-2.73 (-3.98, -1.48)	<0.0001
PEM 2.0%	63	9.49	0.625	-5.78	0.425	-3.65 (-4.84, -2.46)	<0.0001
Pooled PEM (0.5% + 1.0% + 2.0%) ^f	164	9.23	0.366	-5.44	0.287	-3.31 (-4.31, -2.30)	<0.0001
VVSymQ: Study 016							
Placebo	54	9.26	0.666	-2.00	0.474		
PEM 0.125% (control)	54	9.11	0.618	-5.34	0.476	-3.34 (-4.63, -2.04)	<0.0001
PEM 0.5%	60	9.48	0.573	-6.01	0.454	-4.00 (-5.26, -2.74)	<0.0001
PEM 1.0%	57	7.82	0.568	-5.06	0.463	-3.05 (-4.33, -1.77)	<0.0001
Pooled PEM (0.5% + 1.0%) ^f	117	8.67	0.409	-5.53	0.330	-3.53 (-4.63, -2.42)	<0.0001

^a N is the number of patients with both a baseline value and a value at the corresponding visit.

^b Visit 2 (baseline)

^c Least square means from analysis of covariance (ANCOVA) model with treatment group and site as class variables and the corresponding baseline score from the questionnaire as a continuous covariate.

^d 95% Confidence Interval for comparison of PEM versus Vehicle based on adjusted means (least square means from ANCOVA model with treatment group and site as class variables and the corresponding baseline score from the questionnaire as a continuous covariate), unadjusted for multiple comparisons.

^e Two-sided significance level for paired comparisons. ^f Primary efficacy analysis. Note: On the VVSymQ instrument, lower scores and/or negative change scores indicate better outcomes.

Responder analyses:

For Study 015 and Study 016, a clinically meaningful change in symptom burden, as measured by change in VVSymQ score, was evaluated using two responder analyses: Responders-I and Responders-II. Additionally, cumulative distribution of change was also evaluated.

In the Responders-I analysis, the response threshold was calculated as the mean change in the VVSymQ score for all patients who rated their change in symptoms from Baseline to Week 8 as “moderately improved” on the PGIC. This threshold was similar in both studies: -4.66 and -4.60 for Study 015 and 016, respectively. The proportions of responders in the treatment group, using this definition, were significant in both studies. In Study 015, 50% of the patients in the treatment groups (pooled) were responders, compared to 14% of patients in the vehicle placebo group (p<0.0001); and similarly, the responder rate was 52% compared to 23% in Study 016 (p=0.0004), respectively.

In the Responders-II analysis, the response threshold was calculated similarly to the Responders-I analysis, except the responders included patients who rated their change in symptoms from

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Baseline to Week 8 as “moderately improved” or “much improved” on the PGIC. The threshold was similar in both studies: -6.07 and -5.99 for Study 015 and 016, respectively. As expected, slightly fewer patients met the more stringent criterion for this responder definition compared to the Responders-I analysis. However, the differences between the treatment group and the vehicle placebo groups were statistically significant in both studies.

Parameter Study	Study 015 (Placebo, N = 56) (Pooled PEM 0.5%+1.0%+2.0%, N = 165)		Study 016 (Placebo, N = 56) (Pooled PEM 0.5%+1.0%, N = 118)	
	Responders-I ^a n (%)	Responders-II ^b n (%)	Responders-I ^c n (%)	Responders-II ^d n (%)
Placebo	8 (14.3)	4 (7.1)	13 (23.2)	7 (12.5)
Pooled PEM	82 (49.7)	55 (33.3)	61 (51.7)	48 (40.7)
Comparison vs Vehicle ^e	<0.0001	<0.0001	0.0004	0.0002

^a Patients who meet the Responders-I threshold = -4.66 (the mean change in VVSymQ in all patients with a response of 'moderately improved' only on the PGIC in Symptoms)

^b Threshold = -6.07 (the mean change in VVSymQ in all patients with a response of 'moderately improved' or 'much improved' on the PGIC in Symptoms)

^c Threshold = -4.59 (the mean change in VVSymQ in all patients with a response of 'moderately improved' only on the PGIC in Symptoms)

^d Threshold = -5.99 (the mean change in VVSymQ in all patients with a response of 'moderately improved' or 'much improved' on the PGIC in Symptoms)

^e P-values from the Cochran-Mantel-Haenszel (CMH) chi-square test stratified by site.

The results of the individual dose concentrations are provided in the tables below. Note that the sponsor is seeking approval for the 1% dose concentration.

Study 015:

Table 14.2.6.1
Number of Patients Achieving a Clinically Meaningful Change from Baseline in Daily Diary VVSymQ at Week 8 (PGIC in Symptoms)
Efficacy Population

Parameter	Treatment Group, n (%)					Pooled PEM (PEM 0.5%+PEM 1.0%+PEM 2.0%) (N=165)
	Vehicle (N=56)	PEM 0.125% (N=57)	PEM 0.5% (N=51)	PEM 1.0% (N=51)	PEM 2.0% (N=63)	
Responders-I ^a	8 (14.3)	19 (33.3)	24 (47.1)	23 (45.1)	35 (55.6)	82 (49.7)
Comparison vs. Vehicle ^b		0.0235	0.0003	0.0014	<0.0001	<0.0001
Responders-II ^f	4 (7.1)	16 (28.1)	16 (31.4)	13 (25.5)	26 (41.3)	55 (33.3)
Comparison vs. Vehicle ^b		0.0064	0.0021	0.0145	<0.0001	<0.0001

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Study 016:

Table 14.2.6.1
Number of Patients Achieving a Clinically Meaningful Change from Baseline in Daily Diary VVSymQ at Week 8 (PGIC in Symptoms)
Efficacy Population

Parameter	Treatment Group, n (%)				
	Vehicle (N=56)	PEM 0.125% (N=57)	PEM 0.5% (N=60)	PEM 1.0% (N=58)	Pooled PEM (PEM 0.5%+PEM 1.0%) (N=118)
Responders-I ^a	13 (23.2)	25 (43.9)	39 (65.0)	22 (37.9)	61 (51.7)
Comparison vs. Vehicle ^b		0.0254	<0.0001	0.0758	0.0004
Responders-II ^c	7 (12.5)	18 (31.6)	30 (50.0)	18 (31.0)	48 (40.7)
Comparison vs. Vehicle ^b		0.0187	<0.0001	0.0126	0.0002

Reviewer's comments: Although there appears to be a small placebo effect measured by the VVSymQ, the overall treatment effect is substantially larger in the pooled analyses. The results of the individual dosage concentrations for PEM 1.0% in Study 015 is also supportive of this (Responders-I, $p=0.0014$; Responders-II, $p=0.0145$). However, the results from Study 016 showed a smaller effect that was less statistically significant in the Responders-I analysis, with $p=0.0758$. This was unexpected, since the lower dose concentration of PEM 0.5% had a greater proportion of responders in both analyses, and was statistically significant ($p<0.0001$ for both analyses). We recommend that the Division look at this more closely to determine why the higher dose concentration of 1.0% had fewer responders than the lower doses of 0.125% and 0.5% in Study 016. Overall, the results of the responder analyses appear to be reasonable and support that patients experienced a clinically meaningful change in symptoms as a result of using the treatment.

11 KEY REFERENCES FOR MEASURE

Lamping DL, Schroter S, Kurz X et al. Evaluation of outcomes in chronic venous disorders of the leg: Development of a scientifically rigorous, patient-reported measure of symptoms and quality of life. *J Vasc Surg* 2003; 37: 410-9.

Kahn SR, Lamping DL, Ducruet T, et al. VEINES-QOL/Sym questionnaire was a reliable and valid disease-specific quality of life measure for deep venous thrombosis. *J of Clin Epi* 2006; 59: 1049-1056.

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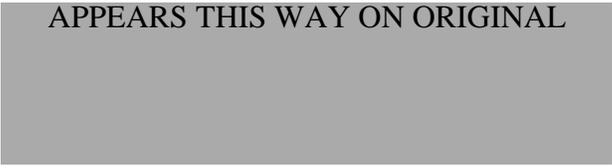
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C. APPENDICES

APPEARS THIS WAY ON ORIGINAL



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Appendix A: Daily Diary for Varicose Veins Symptoms, Activity, and Inactivity Items

ITEM	RESPONSE SCALE	VVSymQ
Please answer the following for the time since waking up today...	N/A	
Since waking up today, how often had you had the following problem in your leg to be treated? Heaviness	None of the Time A Little of the Time Some of the Time A Good Bit of the Time Most of the Time All of the Time	Yes
Since waking up today, how often had you had the following problem in your leg to be treated? Achiness	None of the Time A Little of the Time Some of the Time A Good Bit of the Time Most of the Time All of the Time	Yes
Since waking up today, how often had you had the following problem in your leg to be treated? Swelling	None of the Time A Little of the Time Some of the Time A Good Bit of the Time Most of the Time All of the Time	Yes
Since waking up today, how often had you had the following problem in your leg to be treated? Throbbing	None of the Time A Little of the Time	Yes

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ITEM	RESPONSE SCALE	VVSymQ
	Some of the Time A Good Bit of the Time Most of the Time All of the Time	
Since waking up today, how often had you had the following problem in your leg to be treated? Itching	None of the Time A Little of the Time Some of the Time A Good Bit of the Time Most of the Time All of the Time	Yes
Since waking up today, how often had you had the following problem in your leg to be treated? Heat or burning sensation	None of the Time A Little of the Time Some of the Time A Good Bit of the Time Most of the Time All of the Time	No
Since waking up today, how often had you had the following problem in your leg to be treated? Tingling sensation	None of the Time A Little of the Time Some of the Time A Good Bit of the Time	No

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ITEM	RESPONSE SCALE	VVSymQ
	Most of the Time All of the Time	
Please select your overall activity level since waking up today?	No Activity A Little Activity Some Activity A Good Bit of Activity A Lot of Activity Extreme Activity	No
How much of the time have you spent sitting or standing without moving around since waking up today?	None of the Time A Little of the Time Some of the Time A Good Bit of the Time Most of the Time All of the Time	No
Please answer the following about last night...	N/A	
Last night, how often did you have the following problem in your leg to be treated? Night cramps	None of the Time A Little of the Time Some of the Time A Good Bit of the Time	No

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ITEM	RESPONSE SCALE	VVSymQ
	Most of the Time All of the Time	
Last night, how often did you have the following problem in your leg to be treated? Restless legs	None of the Time A Little of the Time Some of the Time A Good Bit of the Time Most of the Time All of the Time	No
Please answer the following about the past 24 hours...	N/A	
During the past 24 hours, what was the worst Heaviness you had in your leg to be treated?	0 1 2 3 4 5 6 7 8 9 10 None As bad as you can imagine	No
During the past 24 hours, what was the worst Achiness you had in your leg to be treated?	0 1 2 3 4 5 6 7 8 9 10 None As bad as you can imagine	No
During the past 24 hours, what was the worst Swelling you had in your leg to be treated?	0 1 2 3 4 5 6 7 8 9 10 None As bad as you can imagine	No
During the past 24 hours, what was the worst Throbbing you had in your leg to be treated?	0 1 2 3 4 5 6 7 8 9 10 None As bad as you can imagine	No

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ITEM	RESPONSE SCALE	VVSymQ
During the past 24 hours, what was the worst Itching you had in your leg to be treated?	0 1 2 3 4 5 6 7 8 9 10 None As bad as you can imagine	No
During the past 24 hours, what was the worst Heat or burning sensation you had in your leg to be treated?	0 1 2 3 4 5 6 7 8 9 10 None As bad as you can imagine	No
During the past 24 hours, what was the worst Tingling sensation you had in your leg to be treated?	0 1 2 3 4 5 6 7 8 9 10 None As bad as you can imagine	No
During the past 24 hours, what was the worst Night cramps you had in your leg to be treated?	0 1 2 3 4 5 6 7 8 9 10 None As bad as you can imagine	No
During the past 24 hours, what was the worst Restless legs you had in your leg to be treated?	0 1 2 3 4 5 6 7 8 9 10 None As bad as you can imagine	No

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

/s/

JESSICA VOQUI
06/07/2013

LAURIE B BURKE
06/07/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 205098 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Varithena Established/Proper Name: polidocanol Dosage Form: injectable microfoam Strengths: 1%		
Applicant: Provensis Ltd Agent for Applicant (if applicable): BTG International Inc		
Date of Application: February 1, 2013 Date of Receipt: February 4, 2013 Date clock started after UN:		
PDUFA Goal Date: December 4, 2013	Action Goal Date (if different): November 22, 2013	
Filing Date: April 5, 2013	Date of Filing Meeting: March 14, 2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication(s)/Proposed change(s): treatment of incompetent great saphenous veins (GSV), accessory saphenous veins and visible varicosities of the GSV above and below the knee and improvement of the symptoms of superficial venous incompetence and the appearance of visible varicosities in the GSV system.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input checked="" type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input checked="" type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 063420				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>			X	
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1623"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		<p>X</p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

(BLAs/BLA efficacy supplements) including:				
<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the</i>				

<i>supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>			X	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	X			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>			X	
<u>Proprietary Name</u>	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
<u>REMS</u>	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
<u>Prescription Labeling</u>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)			X	
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 2009-06-29	X			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 2012-03-26; 2012-07-31; 2012-12-14	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):			X	Two NA SPAs
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: 2013-03-14

BLA/NDA/Supp #: 205098

PROPRIETARY NAME: Varithena

ESTABLISHED/PROPER NAME: polidocanol

DOSAGE FORM/STRENGTH: injectable microfoam 1%

APPLICANT: Provensis

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

Treatment of incompetent great saphenous veins (GSV), accessory saphenous veins and visible varicosities of the GSV above and below the knee and improvement of the symptoms of superficial venous incompetence and the appearance of visible varicosities in the GSV system.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Michael Monteleone	Y
	CPMS/TL:	Edward Fromm	Y
Cross-Discipline Team Leader (CDTL)	Khin U		Y
Clinical	Reviewer:	Khin U	Y
	TL:	Thomas Marciniak	N
Clinical Pharmacology	Reviewer:	Peter Hinderling	Y
	TL:	Raj Madabushi	N
Biostatistics	Reviewer:	Steven Bai	Y
	TL:	James Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	William Link	Y
	TL:	Albert Defelice	N

Product Quality (CMC)	Reviewer:	Wendy Wilson	Y
	TL:	Kasturi Srinivasachar	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Steve Langille	Y
	TL:		
Facility Review/Inspection	Reviewer:	Vibhakar Shah	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Kimberly Defronzo	Y
	TL:	Irene Chan	Y
OSE/DRISK (REMS)	Reviewer:	Kimberly Lehrfeld	Y
	TL:	Reema Mehta	N

Bioresearch Monitoring (OSI)	Reviewer:	Sharon Gershon	N
	TL:		
Other reviewers	Banu Zolnik (Biopharm)		Y
	Jessica Voqui (SEALD)		Y
	Ann Marie Trentacosti (SEALD)		Y
	Martin McDermott (CDRH)		Y
	Jhumur Banik (CDRH)		Y
Other attendees	Stephen Grant (DCRP)		
	Mary Ross Southworth (DCRP)		
	Steven Hertz (DMPQ)		
	Andrew Durfor (CDRH)		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p><input checked="" type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Division</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): July 1, 2013</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p>	

Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:</p> <p>http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

MICHAEL V MONTELEONE
04/11/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Enforcement B
Vascular and Circulatory Support Devices Branch

DATE: March 8, 2013

TO: Kasturi Srinivasahar, Office of New Drug Quality Assessment, CDER, WO-21, Room 2516

Cc: Ramesh Sood, Office of New Drug Quality Assessment, CDER, WO-21, RM2530
Vibhakar Shah, Office of Compliance, CDER, WO-51, RM4334
Debbie Mesmer, Office of New Drug Quality Assessment, CDER, WO-21 RM2623
Office of Combination Products at combination@fda.gov

THRU: Daniel Walter, Chief, Vascular and Circulatory Support Devices Branch, Division of Enforcement B, Office of Compliance, CDRH, WO-66, Room 3678

FROM: Andrew Durfor, Vascular and Circulatory Support Devices Branch, Division of Enforcement B, Office of Compliance, CDRH, WO-66, Room 3646

SUBJECT: Inter-Center consult requested by Office of New Drug Quality Assessment / CDER. This is a pre-market consult for Polidocanol Injectable Microfoam, NDA 205098.

CONSULT INSTRUCTIONS: Evaluate device manufacturing sites and indicate which sites should be submitted for inspection.

A
3/15/13

Objective

The Office of Compliance at CDRH received a consult request from CDER regarding the Polidocanol Injectable Microfoam (NDA 205098). Drug is a combination product and CDER asked CDRH to evaluate the device manufacturing site and indicate which sites should be submitted for inspection.

Product Description

This product is indicated for treatment of incompetent great saphenous veins, accessory

saphenous veins, and visible varicosities of the great saphenous vein (GSV) systems above and below the knee.

[Redacted] (b) (4)

The product is composed of a canister containing the drug product, a transfer unit which is screwed onto the canister [Redacted] (b) (4) and syringes (single use) for administration.

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/s/

DEBORAH M MESMER

03/22/2013

Entering review into DARRTS on behalf of CDRH/OC reviewer, Andrew Durfor