IMTS # 10943

MEETING MINUTES

Docket #: 76N-052G
Topic: Vaporizer in a Bottle
Sponsor: Lil' Drug Store Products, Inc.

Meeting Request Date: June 23, 2003
Meeting Package Submission: July 16, 2003
Meeting Date: September 11, 2003

Background

Vaporizer in a Bottle (VIAB) is a combination of camphor (3.6 % w/v) and menthol (0.55 % w/v) that has been marketed as an OTC antitussive drug product since 1972. The delivery system is unique from other cough suppressant products. The vapors of the active ingredients are released through evaporation via a wick delivery system at room temperature. This combination of active ingredients in a wick delivery system is not included in the Cough-Cold Combination Final Monograph.

This meeting was requested to discuss what studies are necessary so that the Cough-Cold Combination Final Monograph can be amended to include Vaporizer in a Bottle.

Meeting Attendees

FDA Office of Drug Evaluation V

Brian Harvey, M.D.	Deputy Office Director
John O'Malley	Computer Specialist

Division of OTC Drug Products

Charles Ganley, M.D.	Division Director
Curt Rosebraugh, M.D., M.P.H.	Deputy Director
Daiva Shetty, M.D.	Medical Officer
Marina Chang	Team Leader
Cazemiro Martin	Regulatory Review Chemist/IDS
Michael Benson, P.D., J.D.	Regulatory Review Pharmacist
Gerald Rachanow, P.D., J.D.	Regulatory Counsel
Elaine Abraham	Project Manager

Division of Pulmonary and Allergy Drug Products

Lydia Gilbert-McClain, M.D.	Medical Team Leader
Charles Lee, M.D.	Medical Officer

Division of Biometrics III

Stan Lin, Ph.D.	Statistical Team Leader

Office of Clinical Pharmacology and Biopharmaceutics

Abimbola Adebowale, Ph.D.	Pharmacokinetics Reviewer

Lil' Drug Store, Inc.

James M. Nikrant	Chief Executive Officer
Lorin Reicks	Operations and Regulatory Manager
John Warner	Regulatory Consultant

External Attendee

Armond Welch	AAC Consulting

Meeting Minutes

Cazemiro Martin, FDA, presented an overview of the relevant monograph history of Cough-Cold drug products.

The Cough-Cold Advisory Panel recommended the following two types of clinical studies to establish antitussive effectiveness (41 FR 38312 at 38355; 9/9/76):

Method #1:

- small group of healthy volunteers (10-20 subjects; preferably non-smokers)
- double-blind , crossover design; challenge using irritant aerosol (citric acid)
- determine effectiveness, dose, time responses to experimental-induced cough

Method #2:

- patients with cough due to respiratory disease
- double-blind, controlled; coughs recorded and counted for stated period after giving drug or placebo following a single dose and multiple doses
- long testing period not necessary; effectiveness after 1 or, at most, 2 days

The Panel's recommendations regarding data interpretation are as follows:

1. a minimum of two positive studies based on the results of two different investigators or laboratories
2. clinical studies should employ objective cough-counting techniques for recording the cough reflex
3. two required studies should consist of either:
   - one challenge study with experimentally-induced cough plus a study with cough in respiratory disease or, alternatively
   - two studies by different investigators in patients with respiratory disease. A significant reduction in cough when compared with placebo by acceptable statistical analysis of the data is required

According to 21 CFR 341.14(b), camphor 4.7 - 5.3 % and menthol 2.6 - 2.8 % are permitted for use as topical antitussives as single ingredients formulated in a suitable ointment vehicle. These two single ingredients are also permitted for steam inhalation use. The concentration for steam inhalation use differs [camphor 6.2% (final concentration of 0.10 %) or menthol 3.2 % (final concentration of 0.05 %)].

According to 21 CFR 341.40(u), there is one permitted combination of active antitussive ingredients: camphor/menthol/eucalyptus oil in a suitable ointment vehicle (4.7 - 5.3, 2.6 - 2.8, 1.2 - 1.3 %, respectively). No antitussive combination ingredients in a steam vaporizer are included in the final monograph.

It should be noted that eucalyptus oil is permitted only as part of a combination product. It is non-monograph as an antitussive single ingredient. Also, camphor, menthol, and eucalyptus oil as single and combination ingredients are classified as non-monograph nasal decongestants.

This product (wick system formulation) was discussed in Comment 16 of the Cough-Cold Combination Final Rule (67 FR 78158 at 78164; 12/23/02). The comment:

- requested inclusion of camphor/menthol/eucalyptus oil combination as a permitted combination in a liquid dosage form for antitussive use by evaporation/inhalation at ambient temperatures, and

- proposed to conduct an in vitro bioequivalence study to determine whether the release of vapors from the combination in a liquid dosage form by evaporation through a wick system is bioequivalent to the release of vapors from the same combination in an ointment dosage form rubbed on the chest

The agency's response stated that the "release of vapors from a liquid dosage form by evaporation through a wick system is not comparable to the release of vapors from an ointment dosage form rubbed on the chest of the user" (67 FR 78158 at 78164; 12/23/02).

Additional points on this conclusion were as follows:

- a liquid dosage form that remains stationary and works by evaporation limits mobility of the user to a specific distance from the container and thus, is not comparable to an ointment dosage form

- comparative in vitro studies provide little useful information because of significant differences between the release of vapors from a wick versus release from an ointment

- in vitro studies submitted do not provide adequate information to determine whether it is an appropriate method of demonstrating the bioequivalence of VIAB to VapoRub® ointment under comparative conditions of use

- clinical studies are necessary to demonstrate antitussive effectiveness

Discussion

The following questions were provided for discussion by Lil' Drug Store Products, Inc.:

Meeting Question # 1:

Would successful completion of the in-vitro test, as proposed, support monograph status for VIAB?

<u>FDA RESPONSE</u>:

- **No. Your in vitro comparative study would not provide the information necessary to support efficacy of your product.**

- **See the agency response to Comment # 16 in cough-cold combination FM and agency feedback letter to O'Connor Pharmaceuticals, dated 4/14/92**

- **There are differences in the release of vapors between evaporation from a wick and steam from a vaporizer. Concentration gradients of actives are likely to be different with these two types of products. A significant component of efficacy from steam inhalers could come from mist droplets, which are not generated by a product which is evaporated from a wick.**

- **Vicks VapoSteam® is a single ingredient topical antitussive for steam inhalation and contains only camphor. It does not contain menthol and would not be an appropriate proposed reference drug product for this comparison.**

Meeting Question # 2:

Are there any modifications of the in vitro test procedure the FDA would recommend?

FDA RESPONSE:

We have no recommendations for modifications. An in vitro comparative study would not provide the information necessary to support efficacy of your product.

Meeting Question # 3:

Would successful completion of the in vitro test support monograph status for a product with only a single active (i.e., camphor or menthol) or with the combination of the two?

FDA RESPONSE:

An in vitro comparative study would not provide the information necessary to support efficacy of your product.

Meeting Question # 4:

Would successful completion of the clinical trial, as proposed, support monograph status for VIAB?

FDA RESPONSE:

- **A single clinical cough challenge study will not provide sufficient evidence of efficacy or safety. Evidence should be provided in at least two studies. These studies should be conducted by different investigators or laboratories. The two required studies should consist of either one challenge study and one study in patients with respiratory disease, or two studies in patients with respiratory disease.**

- **The most simple design would be a two-arm study that would compare the cough suppressant efficacy of the following:**

- **VIAB, using camphor/menthol/eucalyptus oil at the same concentrations as in combination topical antitussives in an ointment vehicle [21 CFR 341.40(u)]**

- **Placebo**

- **A multifactorial design would be necessary to establish each ingredient's contribution to the efficacy of the product if concentrations of camphor/menthol/eucalyptus oil are different from those noted in the OTC monograph.**

Meeting Question # 5:

Are there any modifications of the clinical test procedure the FDA would recommend?

FDA RESPONSE:

- **Your proposed clinical study outline is lacking the detail required for a protocol. A detailed protocol should be provided for review if you choose to perform such a study.**

- **Your proposed clinical study outline provides little detail on the citric acid cough challenge procedure. The outline does not indicate if a dosimeter is to be used. Any future protocol should completely describe the challenge procedure, including the source and preparation of the citric acid product to be used.**

- **The proposed study is investigator-blinded, but not subject-blinded. The cough reflex may be voluntarily suppressed. An effort should be made to blind study treatment to subjects, perhaps by including in the placebo a masking agent that is not irritative and does not suppress cough.**

- **Your outline states that the use of antitussive, antihistamine, expectorant, or sympathomimetic agents are prohibited for 24 hours prior to challenge. This period is too short. Antitussives, expectorants, short-acting antihistamines, and sympathomimetic agents should be prohibited for three days prior to challenge. Long acting antihistamines, such as hydroxyzine, cetirizine, fexofenadine, and loratadine should be prohibited for seven days prior to challenge.**

- **It is not clear who will be monitoring and recording coughs, nor is it clear if this person will be blinded to study treatment. These details should be included in any future protocol. The person monitoring and recording coughs should be blinded to study treatment.**

- **Your clinical study outline suggests that only serious adverse events are to be recorded. All adverse events should be recorded, regardless of attribution, degree of severity, or seriousness.**

- **Any future detailed protocol should specify a single primary efficacy endpoint. Multiple secondary efficacy endpoints are acceptable.**

- **Primary and secondary endpoints of the study should be clearly defined. The primary endpoint should be a clinically meaningful reduction of cough count.**

- **The study should clearly define directions for use, i.e., distance at which the drug should be kept, duration, and frequency of the treatments. Labeling of the new product should reflect those conditions.**

- **Subjects entering the study should be asked if they smoke, and the history of their smoking habits should be collected. Smokers and non-smokers should be evaluated separately and combined.**

- **Subjects should receive treatment, one at a time, not together in a room.**

- **The protocol should define the order of the study events: timing of challenges, treatment, informed consent, etc.**

- **Describe the setting in which the study will be conducted, and conditions of the room where the study medications will be given.**

- **All subjects who received at least one dose of the study medication should be included in the safety database.**

- **Specify the timing of assessments with regard to each challenge.**

- **Specify the rescue medication for anticipated, if any, adverse events.**

- **Define the purpose of the tape and pneumotach recordings.**

Meeting Question # 6:

Would successful completion of the clinical trial support monograph status for a product with only a single active (i.e., camphor or menthol) or with the combination of the two?

FDA RESPONSE:

As noted above, evidence of efficacy should be provided in at least two studies conducted by different investigators or laboratories. The two required studies should consist of either one challenge study and one study in patients with respiratory disease, or two studies in patients with respiratory disease. This is true regardless of whether the product has a single ingredient or a combination of ingredients.

Lil' Drug Store Products, Inc. had the following additional questions/comments:

Since steam inhalation is approved for single ingredient use, if VIAB were to be reformulated as a single ingredient and used in the same strength and distance as steam, would clinical studies still be required?

FDA Response:

Because of differences between wick and steam, even if controlled for distance, clinical studies would be necessary.

What is the status of VIAB while clinical trials are being conducted?

FDA Response:

The product can continue to be marketed until the effective date of the Cough-Cold Combination Products final monograph (December 23, 2004). A request for a deferral of the implementation date can be made when data are submitted.

How should data be submitted?

FDA Response:

Submit the protocol for comments prior to proceeding with the study. Submission of the protocol is encouraged as early as possible. The protocol and data should be submitted to the docket.

Can data be submitted in stages?

FDA Response:

The complete report should be submitted at one time, rather than in stages.

FDA noted that oil of eucalyptus is listed as an inactive ingredient on the label. The agency requested that the concentration of oil of eucalyptus as well as oil of white camphor be provided. The sponsor agreed to send that information to the agency.

Elaine Abraham
Minutes Preparer

Charles Ganley, M.D.
Concurrence