CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-387

OTHER REVIEW(S)

22-387 TYVASO® (treprostinil) Inhalation Solution

Project Manager Overview

NDA 22-387 (pulmonary arterial hypertension)
TYVASO® (treprostinil) Inhalation Solution
Pharmacologic Class: Prostacyclin Analogue
Combination Product: Drug + Device
Chemical Classification: New formulation (chemical type 5)
Orphan Designation

Background:

Remodulin® (treprostinil) for subcutaneous (NDA 21-272) and intravenous (NDA 21-272/s-002) administration was originally approved under Subpart H on May 21, 2002 (NDA 21-272) and November 24, 2004, respectively.

The sponsor of Remodulin, United Therapeutics, submitted a New Drug Application (NDA) for Tyvaso® (treprostinil) Inhalation Solution 0.6 mg/mL (supplied as 2.9 mL ampules) on June 30, 2008. The studies were conducted under IND 70,362. The sponsor *proposed* to market the product for treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III — symptoms (same indication as Remodulin); however, the agreed upon indication will include use in Class III only. b(4)

The dosage and administration section of the labeling proposes four separate inhalation sessions per day (while awake). Each breath is expected to deliver a dose of approximately 6 mcg per breath. Initial treatment would begin with three breaths (18 mcg) and the maximal target dose per session is 54 mcg (9 breaths).

The Tyvaso Inhalation System involves use of a never-before cleared/marketed nebulizer device. The device, known as the Optineb IR, a portable ultrasonic nebulizer, was submitted under the NDA. DCRP consulted CDRH including a bioengineer and a human factors analyst.

The Division reviewed this NDA under the Good Review Management Principles and Practices—the NDA was assigned a Standard review (10-month clock), however, a 3-month clock extension was granted based on submission of new information related to the device.

Note that the sponsor plans to implement what appears to be an extensive hands-on training program for patients receiving the Tyvaso Inhalation System (drug/device) where nurses train patients one-on-one either in a clinic setting or at the patient's home. Also, patients will be able to obtain the product only from specialty pharmacies (i.e., the product is not available through typical pharmacy distribution channels).

NDA Reviews and Memos

Division Director's Memo #2
Dr. Norman Stockbridge; July 28, 2009
In his second memo, Dr. Stockbridge recommends approval.

Division Director's Memo #1
Dr. Norman Stockbridge; April 25, 2009
In Dr. Stockbridge's initial DD memo, he recommended a Complete Response based on issues relating to manufacture of the drug substance (facility inspections), biocompatibility of the

nebulizer parts that come into human contact, and device-related problems. Although a Complete Response action was recommended, in response to the Division's request, the sponsor submitted several amendments late in the review cycle (March/April) that, per the Division's decision, triggered a 3-month clock extension. Therefore, no action had been taken with respect to the original PDUFA goal date, April 30, 2009. Adding three months to the PDUFA clock made the new goal date July 30, 2009.

CDTL Memo #2
Dr. Avi Karkowsky; July 27, 2009
Dr. Karkowsky notes that there are problems with the device, however, many of the identified problems will be addressed through PMC 2, 3, and 4 (see approval letter). To address the inadequacies, the Division and the sponsor agreed to a timeline (see action letter) which would allow for marketing of the current version of the device for some period of time (i.e., < 2 years). Given his concerns for pulmonary toxicity based on human and animal data provided in the NDA, Dr. Karkowsky requested that the sponsor capture and track adverse events related to pulmonary toxicity via a postmarketing requirement (PMR).

CDTL Memo #1
Dr. Avi Karkowsky; April 19, 2009
Dr. Karkowsky recommended a complete response for various reasons, some of which are:

- The device seems complex and cumbersome to assemble, use and clean
- An adequate human factors study had not been completed (see CDRH's review)
- Biocompatibility data had not been submitted/reviewed
- Inspection facilities had not received an overall acceptable recommendation
- The benefit (increase in 6MWD) was relatively small and wanes at the interdosing interval; he also does not think the inhaled route should be automatically substituted for the SC/IV route of administration

Clinical Review; April 3, 2009
Dr. Avi Karkowsky
Recommended Action: Approvable (pending issues identified in CDTL memo)
Dr. Karkowsky emphasizes that Tyvaso was studied in patients on background therapies including sildenafil and bosentan and such information should be included in the indications section of the labeling. Furthermore, the waning of the treatment effect during the interdosing interval should be noted as well. His major concern regarding safety included adverse events related to irritation of the oro-nasopharynx and respiratory tree.

QT Study; January 30, 2009
Interdisciplinary Review Team for QT Studies
The study failed to exclude a 10 ms increase in the QTc interval (results below).

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Treprostinil sodium (54 mcg and 84 mcg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Treprostinil sodium 54 mcg	0.083	6.4	(3.5, 9.4)
Treprostinil sodium 84 mcg	0.083	8.5	(5.8, 11.3)
Moxifloxacin 400 mg*	3	8.2	(5.8, 10.7)

* Multiple endpoint adjustment is not applied. The largest lower bound after Bonferroni adjustment for 3 timepoints is 5.1 ms.

Statistical Review; April 7, 2009
Dr. John Lawrence
Dr. Lawrence notes that the primary endpoint of the study was change in exercise capacity at week 12 as measured by peak 6MWD. There was an approximately 20 m (95% CI 8, 33) difference between treatment and placebo in 6MWD (p=0.004). Looking across various subgroups, treatment effects appeared to be larger in the following subgroups of patients: those between 18-45 years of age; those whose baseline walk distances were in the bottom quartile (smallest baselines); and patients from the "rest of the world" (i.e., outside North America).

Clinical Pharmacology; March 24, 2009
Dr. Robert Kumi
Recommended action: Approval pending confirmation from CDRH on the reliability (precision and accuracy) that the device can deliver the dose reported in the PK studies.
In some studies, some subjects had undetectable or low treprostinil exposure compared to other subjects. The reason for these low exposures is unclear.

Pharmacology Review; June 24, 2008
Dr. Xavier Joseph
Recommended action: Approval

In his review, Dr. Joseph makes several recommendations for changes to the labeling but has no recommendations for additional nonclinical studies.

Chemistry Review #2; July 23/24, 2009
Dr. Monica Cooper
Recommended action: Approval
See review for details.

Chemistry Review #1; March 24, 2009
Dr. Monica Cooper
Recommended action: Complete Response because of pending issues as noted below.

1) All drug substance information is referenced to NDA 21-272 (Remodulin Injection). A supplement for a new treprostinil drug substance manufacturing facility and — process is currently pending (NDA 21-272/SCM-010). The previous treprostinil drug substance manufacturing site — was closed in 2006. Given that no other drug substance manufacturer is provided in this submission, the current NDA cannot be approved until the supplemental NDA 21-272/SCM-010 is approved. b(4)

2) An information request letter was sent to the applicant on 13-Jan-2009 outlining the CMC information needed to complete this application. The Amendment dated 25-Feb-2009 included a partial response to these issues. An in-use stability study of the drug product in the proposed Optineb nebulizer has not been completed and submitted for our review.

3) Evaluation of the Optineb nebulizer was consulted to CDRH. CDRH has not provided a recommendation at this time. However, an information request was sent to the applicant on 03-Mar-2009 that included several device issues. These issues are currently pending.

4) The Office of Microbiology has not provided a recommendation on the sterility assurance of the drug product.

The Office of Compliance has given an acceptable recommendation for the manufacturing and testing facilities.

Microbiology Review; March 24, 2009
Dr. John Metcalfe
Recommended action: Approval

DMEPA Review #2
In a review dated July 1, 2009, DMEPA found the proposed tradename, Tyvaso, acceptable.

DMEPA Review #1
In a review dated February 19, 2009, the Division for Medication Error Prevention and Analysis found that the proposed trade name Tyvaso does not appear to be vulnerable to name confusion that could lead to mediation errors.

Division of Scientific Investigations (DSI)
April 23, 2009; January 8, 2009
Two sites were inspected as part of a data audit in evaluation of this NDA:

- Numerous discrepancies were noted at Dr. McLaughlin's site and DSI did **NOT** consider the data to be reliable (OAI).
- Dr. Bourge appeared to have conducted the study adequately and DSI considered the data reliable from this site (NAI).

CDRH Review #2
Mr. Sugato De; Mr. Ron Kaye
Mr. De reviewed the biocompatibility information and found it acceptable; however, neither CDRH reviewer found the usability analysis and human factors study to be adequate. They also provide recommendations for changes to the proposed labeling.

CDRH Review #1
Mr. Sugato De; Mr. Ron Kaye
The reviewers in the Center for Devices and Radiological Health (CDRH) do not find the proposed device to be approvable (see review for details).

Action Items: An approval letter will be drafted for Dr. Stockbridge's signature. The approval letter will include one PMR related to pulmonary toxicity and three PMCs related to re-engineering of the device. Labeling, including the PI, PPI, and instructions for use (IFU), is being finalized.

by Dan Brum, Pharm.D., RAC
July 29, 2009

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22387	ORIG 1	UNITED THERAPEUTICS CORP	TREPROSTINIL FOR INHALATION

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

/s/

DANIEL BRUM
07/29/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Anesthesia and Respiratory Devices Branch
Division of Anesthesiology, General Hospital, Infection Control and Dental Device
Office of Device Evaluation
9200 Corporate Boulevard
Rockville, MD 20850

NDA 22-387 – Regulatory Device Review

Date: June 10, 2009
To: Daniel Brum, Regulatory Project Manager (OND/ODEI/DCRP)
From: Sugato De, Biomedical Engineer (ODE/DAGID/ARDB), Lead Reviewer
Ronald Kaye, Human Factors Specialist (ODE/DAGID/GHDB)

Applicant: United Therapeutics Corporation
Device Name: Optineb-IR Ultrasonic Nebulizer (Tyvaso Inhalation Solution)
Indication: Pulmonary Hypertension

A. Executive Summary

In NDA 22-387, United Therapeutics Corporation has proposed a novel combination product intended for the delivery of treprostinil sodium (Tyvaso®) to patients with pulmonary arterial hypertension (PAH). Tyvaso is administered in a home-care setting to patients using the Optineb-IR Ultrasonic Nebulizer, manufactured by NebuTec.

In this regulatory consult, the applicant's responses to deficiencies raised in the April 1, 2009 device consult will be reviewed. Specifically, the remaining concerns raised in the aforementioned letter relate to the completion of ongoing biocompatibility tests, the adequate completion of an adequate usability analysis, and the updated labeling for the proposed device. This memorandum includes the review of the biocompatibility test reports submitted for review on April 29, 2009, the Human Factors Study submitted on April 17, 2009 and the updated labeling submitted on May 7, 2009.

The primary remaining concern at this point relates to the adequate completion of a comprehensive usability analysis incorporating the evaluation and prioritization of user-related risk. Following this evaluation, it is recommended that the applicant perform a comprehensive human factors study demonstrating the safe and effective simulated-use of the Optineb-IR device in an environment that approximates the intended home-care setting. The purpose of this study will be to evaluate the severity of the risks anticipated in the initial usability analysis, and to identify user-related risks that may have been unanticipated by the applicant. At the conclusion of these usability evaluations, the applicant should propose adequate mitigation measures for the identified user-related risks, and may be expected to modify and revalidate the proposed device as necessary to alleviate safety-related concerns regarding its use.

Recommendations:

- The biocompatibility evaluation of the device has been adequately completed, and the findings have demonstrated that the proposed device is biocompatible in accordance with ISO 10993-1.

- The Human Factors Study submitted by the applicant on April 17, 2009 is insufficient and does not adequately address any of the specific device-related concerns communicated to the applicant.

  We defer to CDER's clinical review team regarding appropriate timing for the completion of a comprehensive usability analysis and human factors study. From a device review perspective, we cannot recommend the approval of the proposed drug/device delivery system without the completion of a comprehensive usability and human factors study as described to the applicant in the March 25, 2009 letter. In addition, as noted in the previous consult, it is our position that a pharmokinetic analysis is warranted to measure the level of drug being inhaled by the patient per each nine-breath administration cycle.

  However, if CDER determines that the clinical risk associated with potential overdose or underdose of inhaled treprostinil from the device is minor compared to the relative benefit associated with the availability of the product to the intended population, then the usability may be conducted as a post-market requirement.

- The applicant's proposed labeling is incomplete, and should be revised.

  Because the Optineb-IR has not been cleared as a general-purpose nebulizer in the United States, and is proposed in the current submission solely for the delivery of inhaled treprostinil, we recommend that the Instructions for Use should be tailored specifically to the use of the proposed device to deliver treprostinil. A comprehensive IFU should include assembly instructions for the device, clear instructions to the patient in using the proposed device to delivery treprostinil, and relevant cleaning and maintenance information.

- The name of the device is not under the regulatory jurisdiction of the Office of Device Evaluation. If you seek further guidance on this matter, please contact the Office of Combination products.

B. Device Description

The Optineb®-IR Nebulizer is a device intended for single patient use in the administration of inhaled treprostinil. The nebulizer operates ultrasonically by energizing a piezoelectric transducer at 2.4 MHz. This action collimates distilled water stored in the water reservoir, thus energizing liquid medicine stored in the medicine cup and creating an aerosolized cloud of medication to be delivered to the patient. The dome and baffle components of the nebulizer are designed to control the size of the particles that are emitted from the device. The nebulizer's software responds by providing visual and audible signals to the patient synchronizing the patient's breathing with the nebulization process. The Optineb-IR performs this operation for three consecutive cycles, and dispenses the prescribed dosage at a specified particle size.

The Optineb®-IR consists of a low voltage, . [redacted] electronic control unit, plastic nebulizer components which are reusable for up to [redacted] days, daily disposable medicine cups, and daily disposable inhalation and exhalation filter media.

The Optineb®-IR may be powered by one of three methods:

- A TUV Recognized component (IEC60601-1 & EN60601-1-2) [redacted] VAC power supply, or
- A rechargeable battery pack that my be used in conjunction with the aforementioned power supply, or
- A 12VDC automobile (cigarette lighter) adapter.

b(4)

Treprostinil (15AU81, UT-15) is a stable tricyclic benzindene analogue of the naturally occurring prostacyclin, PGI2 (epoprostenol), a member of the eicanosoid family of autocoids; these compounds occur widely in tissues and have important pharmacological properties with potent activity, especially on the cardiovascular system and smooth muscle. Tyvaso® (treprostinil sodium) Inhalation Solution, 0.6 mg/mL, has been developed as a treatment for pulmonary arterial hypertension (PAH), an orphan disease with a global prevalence of approximately 50,000-100,000 patients.

The recommended dose of Tyvaso is up to nine breaths (54 micrograms) per administration and up to 4 administrations per day; i.e., up to 36 breaths per day, with a maximum dose of twelve breaths (72 micrograms) per administration. The maximum theoretical aerosol concentration of nebulized treprostinil in Tyvaso is [redacted], although the actual aerosol concentration is considerably lower.

b(4)

The Optineb-IR device is not a general-purpose nebulizer, and is intended exclusively for use with treprostinil inhaled solution. The applicant has not submitted a separate 510(k) Premarket Notification for the device, and all device-related information is included in the context of IND 70,362 and NDA 22-387. As such, the device is not currently cleared for any intended use in the United States, and the current submission is solely attempting to validate its use with Tyvaso Inhalation Solution.

C. Biocompatibility Review

Potential device-related effects were evaluated in a program of biocompatibility studies with extracts of the nebulizer materials that come in contact with the drug.

The testing program was determined by reference to ISO 10993-1.

There are three different materials of construction in the ventilatory pathway, as shown below.

Device Components in the Ventilatory Pathway

Device Part	Material of Construction
Medicine Cup	
Sealing O-Ring	
Remaining Parts	

b(4)

The study materials were provided for testing. The studies and study references are listed in the summary below. Updated biocompatibility documentation, including test reports for studies that were previously listed as "ongoing," was provided for review on April 29, 2009. b(4)

The required testing was determined in accordance with ISO 10993-1 for Tissue/Bone/Dentin communicating, chronic exposure devices. This testing includes cytotoxicity, intracutaneous reactivity, sensitization, genotoxicity, and implantation on all device parts in the ventilatory pathway.

Since the mouthpiece comes into direct contact with the patient, this part requires sub-chronic toxicity and intracutaneous reactivity (irritation) testing as well.

The results of the testing are discussed below.

Cytotoxicity

The MEM Elution test was designed to determine the cytotoxicity of extractable substances. An extract of the sample was added to cell monolayers and incubated. The cell monolayers were examined and scored based on the degree of cellular destruction. The samples are scored against a set of controls on a scale of 0-4. The sample meets USP requirements if all results are Grade 2 or less.

All the tested components met the requirement.

Intracutaneous Reactivity (Irritation)

The Intracutaneous Reactivity test was designed to determine if any chemicals that may leach or be extracted from the test article were capable of causing local irritation in the dermal tissues of rabbits. The device components were extracted per protocol against saline solution and cottonseed oil. The resulting extracts were then used for testing. All of the device components in both extracts met the ISO 10993-1 requirements and were determined to be non-reactive.

Sensitization

This test is designed to evaluate the allergenic potential or sensitizing capacity of a test article. Extracts of the test material are tested as potential contact allergens in guinea pigs. All of the device component materials specified in the table above met the ISO 10993-1 requirements for sensitization.

Implantation

The purpose of this study is to evaluate the local effects of a test article in direct contact with living skeletal muscle tissue. Implantation studies were performed by the manufacturer of the component, Similar testing has also been completed for the medicine cup and sealing ring components of the proposed device. b(4)

All tests have demonstrated that the materials that the materials are biocompatible as per ISO 10993-1.

Genotoxicity

This test is designed to evaluate potential genetic effects of the test articles. Ames mutagenicity testing was performed by the manufacturer of the component, r. The material met the ISO 10993-1 requirements for this test.

b(4)

Genotoxicity testing has also been completed for the medicine cup and sealing ring components of the proposed device. Mouse lymphoma testing and chromosomal aberration testing were also completed for the proposed device, and have demonstrated that the patient-contacting materials of the proposed device are not genotoxic.

Sub-Chronic Toxicity

The purpose of this study is to evaluate the systemic toxicity of leachable compounds from the test article. This test is intended for medical devices with a contact duration categorized as permanent (greater than 30 days). This testing is required only for the mouthpiece, and has been completed.

The test report demonstrates that leachable components from the test article were within measurable limits. b(4)

Review Comments:

All protocols and acceptance criteria provided by the applicant are adequate in reference to ISO 10993-1, and completed test reports have been provided demonstrating the biocompatibility of the proposed device.

D. Human Factors Review

Human Factors Device Consult Reviewer: Ron Kaye (ODE/DAGID/GHDB)

In the initial review of the submission, several user-related concerns were identified by the Agency and were communicated to the applicant in a letter dated March 3, 2009. In this letter, the Agency communicated a concern to the applicant that the current design of the device and the materials supporting its use (e.g. user manual) could possibly induce or allow use-errors that may compromise the user's ability to deliver medication properly and could thereby pose significant risks.

Please see Appendix 1 below for the full test of the human factors-related deficiency sent to the applicant on March 3, 2009.

Among the major concerns identified by the Agency was whether users can properly dose themselves with a total of nine breaths using the currently designed breath counter mechanism. This counter counts only up to three and the patient must restart the device two additional times to receive the required nine breaths.

Additional risks include the following:

- Possible risk associated with delivery of less than the prescribed dose given the apparently challenging requirement for the user to take nine deep breaths within the specified time limit of ninety seconds.
- Whether the inhalation or exhalation into the mouthpiece triggers a change in the count displayed by the breath-counter mechanism, whether this trigger is time-related, and whether the user needs to be aware of how this process operates to ensure proper use and delivered dosage.
- The ability of users to correctly assemble your device under conditions consistent with home-use to include proper physical connection of device components and loading of appropriate levels of medication into the cup.

On April 17, 2009, the applicant submitted a preliminary Human Factors Study for review.

The Human Factors Usability Test report is evaluated here with respect to the comments provided to the applicant following review of the Draft Usability Test Protocol on March 3, 2009 (see Appendix 1).

1. Essential Components of User Interaction

The simulated use performed in the Usability Test was modified to include breathing through the device and included placing the mouth on the mouthpiece. The components of interaction between the user and the device were developed into a "Use Error Checklist" presented as Appendix D. Although the checklist items are extensive and appear to be comprehensive, they are not prioritized and results with respect to the clinical impact of errors found using these checklist items is not presented in the test report. The Agency needs to understand the relative risk of user performance and use errors on the health and well being of the device user to adequately evaluate the safety of the use of your device. See recommendation (below).

2. Training

The training process included the use of Competency Test to screen participants. Given that the population of users evaluated excluded those who did not pass the Competency Test and that passing this test is considered essential for safe and effective use of the device, the requirement of passing the test prior to being allowed to use the device should be highlighted in the IFU including the Package Insert. If this is not clearly stated, then the entire test results are biased and non-representative of actual intended users. Discussion of testing results, in addition to previous and subsequent comments, should include a discussion of the realism of a 2-hour training course for intended users and assurance to the Agency of how this will occur and why it is of realistic to expect that general users will receive the same level of training used in this study. See recommendation (below).

3. Screening Participants

The method used for screening participants involved in the Usability Study was modified from the draft protocol such that it is acceptable.

4. Testing Procedure

The method used for Testing Procedure involved in the Usability Study was modified from the draft protocol such that it is acceptable.

5-7. Data Reduction, Analysis, and Reporting,
Measures of User Performance and Acceptable Performance Criteria (Pass/Fail Criteria), and Modifications to Device Design

The reporting findings include the frequencies of each error recorded and a reference Task number during which the error occurred. There were 76 use errors reported with a frequency of occurrence ranging from 10 occurrences to 1. The errors were associated with 12 of the 13 tasks evaluated.

Further interpretation of the findings with respect to the priority of the findings in terms of risk to the intended population of users, actions and plans associated with identified risks as necessary was deferred to UTC who developed a separate document linking use errors to risk analysis. Review under this heading corresponds includes that document: "*Human Factors Use-Related Risk Assessment.*" Acceptable/unacceptable performance is not identified in either the test report or the use-risk assessment document. The latter document assigns risk levels to each use error found according to probability of occurrence and severity of outcome. Overall, the testing and analysis is incomplete in a number of ways:

1. Subjective assessment of device interaction that focuses on high-priority aspects of device use is considered an important aspect of Usability or Human Factors evaluation. No subjective assessment data was collected in the study and was not included in the evaluation of the use-safety of the device.
2. That the use error involving a user who took 27 breaths instead of 9 in the study, as well as 6 other cases involving more or less breaths than specified in the task instructions represents an "acceptable" risk level is questionable and appears that its assessment is questionable (see next).
3. If a use error could result in significant harm, assessment of a probability of "low" given the relatively small number of uses involved in this study is difficult to justify. It is likely that a confusion of definition exists between the concept of "acceptably low" and "relatively low".
4. The issue of over- and under dosing is not well captured in the risk assessment document in which risk is assigned according to individual breaths and cycles. Overall breath count being high or low (misdosing) does not appear. This has caused such errors to be considered in other sub-tasks that do not bear directly on over- and under-dose for the entire treatment and the clarity of this seemingly important and central issue is obscured due to the methodology used in assessing its risk.

Review Comments:

This study is insufficient and does not adequately address any of the specific device-related concerns previously communicated to the applicant. We recommend that the usability analysis and human factors study be completed in accordance with the recommendations given to the applicant on March 3, 2009.

Given the concerns cited above, the risks associated with the use of the device cannot be mitigated solely with modifications to the training protocol or labeling (Level 2) or with the potential for design changes. These measures leave the question of the effectiveness of the proposed modifications unanswered. Accordingly, these risk definitions are not acceptable for device use since it cannot be accurately determined whether or not they will be effective. Use safety is not considered to be validated from a device review perspective unless the study is expanded to cover mitigation strategies in order to demonstrate that they are effective. For the Agency to adequately understand the risks associated with the use errors identified and their associated mitigation measures requires that we review results of an evaluation that includes this information. Therefore the applicant should provide the results of an additional study that address these and the other concerns contained in this review of your usability test.

As of this review, the applicant has not performed an acceptable Usability Analysis incorporating the evaluation and prioritization of user-related risk. Following this evaluation, it has been recommended that the applicant perform a Human Factors Study demonstrating the safe simulated-use of the Optineb-IR device in an environment that approximates the intended home-care setting. As stated in the March 3, 2009 letter (See Appendix 1), the purpose of this study is to evaluate the severity of the risks anticipated in the initial Usability Analysis, and to identify user-related risks that may have been unanticipated by the applicant. In the end stages of the study, the applicant should propose adequate mitigation measures for the identified user-related risks, and may be expected to modify and revalidate the proposed device as necessary to alleviate safety-related concerns regarding its use.

E. Labeling Review

A summary of the labeling information for the Tyvaso Inhalation Solution was provided for review in NDA 22-387. The information is provided in the form of a User's Manual, in which the device is described in detail, including complete descriptions of all components and optional accessories.

Comprehensive instructions are given regarding how to assemble the nebulizer, how to connect the nebulizer to the power supply, how to fill the medication, and how to operate the nebulizer. Cleaning instructions are provided for the nebulizer chamber lid, continuous filling equipment, nebulization chamber and the mouthpiece of the device. For each part, cleaning, disinfection, and machine washing instructions are provided. Troubleshooting information for various faults is included in the manual, including potential causes and mitigations. Problems covered include insufficient nebulization, failures in the power indicator on the face of the device, and overflow of medication from the medication cup.

Electrical emissions and immunity information are also provided, and will be discussed in further detail.

Revised copies of the Instructions for Use and Patient Package Insert were provided by the applicant on May 7, 2009 in response to the deficiency below:

"*In the initial review of the supplied User's Manual, the Agency concluded that the assembly and usage instructions given would be too difficult for patients and users of the device to comprehend. Additionally, the manual in its present form does not include any information about the drug, including its indications for use, side effects, etc.*

In lieu of the OPTINEB-IR device user manual that you have proposed, the Agency recommends that the applicant instead submit (1) a Patient Package Insert (PPI) and (2) Instructions For Use (IFU). The PPI is intended to focus primarily on the drug product itself, whereas the IFU would focus on the device. PPIs are intended to enhance appropriate use of medications and provide important risk information to patients; the information should be consistent with the information presented in the full prescribing information. IFUs are intended to support the appropriate use of your device.

The following sections with diagrams should be considered for inclusion:

- *Preparing For Your Treatment,*
- *Using your OPTINEB-IR,,*
- *"Maintenance & Cleaning"*

Review Comments:

Following the review of the updated labeling, the following concerns remain from the device-perspective:

- Optineb-IR has not been cleared as a general-purpose nebulizer in the United States, and is proposed in the current submission solely for the delivery of inhaled treprostinil. As such, we recommend that the Instructions for Use should be tailored specifically to the use of the proposed device to deliver treprostinil. A comprehensive IFU should include assembly instructions for the device, clear instructions to the patient in using the proposed device to delivery treprostinil, and relevant cleaning and maintenance information.

  In addition, it is recommended that the IFU include a complete range of drug and device specifications. These would include, but are not limited to, the prescribed dosage specifications in terms of micrograms of drug, the mass median aerodynamic diameter (MMAD) of the delivered drug, the geometric standard deviation of the MMAD and the percent of drug dose delivered which falls in the respirable fraction. These specifications are intended to provide both the caregiver and the patient with an accurate representation of the dosage capacities of the integrated combination product.

- Given the current design of the Optineb-IR, both underdose and overdose of the drug remain significant device-related risks. As such, please provide specific caution and warning statements in the revised IFU to address these concerns. Specifically, it should be noted that if the given instructions are not followed in detail, the patient may be underdosed or potentially may receive no treatment at all, and as such would not receive the complete therapeutic benefit of treprostinil. On a related note, the patient should be instructed to contact their healthcare providers in the case that expected symptomatic benefits of the drug are not observed. In addition, for the purposes of avoiding potential overdose, the user should be cautioned against exceeding a total of nine breaths per administration cycle.

F. Review Conclusions

The biocompatibility evaluation of the device has been adequately completed, and the findings have demonstrated that the proposed device is biocompatible in accordance with ISO 10993-1.

The Human Factors Study submitted by the applicant on April 17, 2009 is insufficient and does not adequately address any of the specific device-related concerns communicated to the applicant. Overall, the study performed by the applicant did not incorporate the recommendations and comments communicated both in writing and via teleconference to the applicant on March 25, 2009.

Following review of the device component of the combination product, we have remaining engineering concerns regarding accurate dose administration by the device without the completion of a comprehensive usability and human factors study as described to the applicant in the March 25, 2009 letter. In addition, as noted in the previous consult, it is our position that a pharmokinetic analysis is warranted to measure the level of drug being inhaled by the patient per each nine-breath administration cycle.

However, following consultation with CDER's clinical review team, it is our understanding that the initial clinical study performed by the applicant demonstrated a measurable symptomatic benefit from using the device and that device introduces a means of administration for treprostinil that may be preferable for many patients. In addition, the CDER clinical review team indicated that underdose and overdose from the device, both of which are currently considered device-related concerns, do not pose clinical risks to the safety of the patients who are exposed to the product. Taking this information into consideration, we acknowledge that the recommended usability studies and human factors evaluations may be performed as a post-market requirement. Please note that the review path should proceed in a way that ensures that the aforementioned tests are completed by the applicant in a timely manner, and that potential device modifications are made as necessitated by the usability analysis.

The applicant's proposed labeling is incomplete, and may require further revision. Because the proposed device has not been cleared as a general-purpose nebulizer in the United States, and is proposed in the current submission solely for the delivery of inhaled treprostinil, we recommend that the Instructions for Use should be tailored specifically to the use of the proposed device to deliver treprostinil. A comprehensive IFU should include assembly instructions for the device, clear instructions to the patient in using the proposed device to delivery treprostinil, and relevant cleaning and maintenance information.

G. **Outstanding Deficiencies**

After review of the most recent information, the following issues have been identified and should be addressed with additional information by the applicant.

The following concerns may be communicated directly to the applicant:

1. On April 17, 2009, you provided a preliminary human factors study that did not sufficiently address the device-related concerns raised in our letter dated March 3, 2009. Specifically, the proposed study does not include a comprehensive usability analysis incorporating the evaluation and prioritization of user-related risk and does not demonstrate the safe and effective simulated-use of the Optineb-IR device in an environment that approximates the intended home-care setting.

   In addition, please note that the risks associated with the use of the device cannot be mitigated solely with modifications to the training protocol or labeling (Level 2) or with the potential for design changes (Level 3). These risk definitions are not acceptable for device use since it cannot be accurately determined whether or not they will be effective. Use safety is not considered to be validated unless the study is expanded to cover mitigation strategies in order to demonstrate that they are effective. For the Agency to adequately understand the risks associated with the use errors identified and their associated mitigation measures requires that we review results of an evaluation that includes this information.

   Please refer to the guidelines presented in the March 3, 2009 letter, and perform a comprehensive usability analysis and human factors evaluation in accordance with the cited recommendations.

2. Optineb-IR has not been cleared as a general-purpose nebulizer in the United States, and is proposed in the current submission solely for the delivery of inhaled treprostinil. As such, we recommend that the Instructions for Use should be tailored specifically to the use of the proposed device to deliver treprostinil. A comprehensive IFU should include assembly instructions for the device, clear instructions to the patient in using the proposed device to delivery treprostinil, and relevant cleaning and maintenance information.

   In addition, in accordance with requirements for general-purpose nebulizers, it is recommended that the IFU include a complete range of drug and device specifications. These would include, but are not limited to, the prescribed dosage specifications in terms of micrograms of drug, the mass median aerodynamic diameter (MMAD) of the delivered drug, the geometric standard deviation of the MMAD and the percent of drug dose delivered which falls in the respirable fraction ( ). These specifications are intended to provide both the caregiver and the patient with an accurate representation of the dosage capacities of the integrated combination product. b(4)

3. Given the current design of the Optineb-IR, both underdose and overdose of the drug remain significant device-related risks. As such, please provide specific caution and warning statements in the revised IFU to address these concerns. Specifically, it should be noted that if the given instructions are not followed in detail, the patient may be underdosed or potentially may receive no treatment at all, and as such would not receive the complete therapeutic benefit of treprostinil. On a related note, the patient should be instructed to contact their healthcare providers in the case that expected symptomatic benefits of the drug are not observed. In addition, for the purposes of avoiding potential overdose, the user should be cautioned against exceeding a total of nine breaths per administration cycle.

Appendix 1: Previous Human Factors Deficiency

On March 3, 2009, the following deficiency was sent to the applicant regarding human factors following the review of their proposed testing protocol:

1. Please refer to your June 27, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tyvaso (treprostinil) Inhalation Solution. We also refer to our letter dated March 3, 2009 and your submission dated March 25, 2009. We have completed our review of your protocol entitled "Summative Usability Test of TYVASO Inhalation System" and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

   The March 3, 2009 letter expressed our concerns regarding the current your application specifically pertaining to the design of the device and the requirement for users to appropriately dose themselves with the inhalation solution. In the sub-section "Device-Human Factors," we provided examples of areas of user-device interaction that appeared to be potentially problematic for home users. We also requested that you perform a comprehensive analysis of use-related risk and provided you with the web-address of the CDRH guidance on managing use-related risk for medical devices.

   Your "draft" protocol describes a procedure for a "summative usability test" that involves a form of simulated use of your device to include 15 to 20 participants to represent intended users. Review of this protocol indicates that it will not be sufficient to generate adequate test results in its current form to indicate that your device can be used safely and effectively as per its intended use. Deficiencies in your protocol and recommendations for its modification are as follows:

   1. Essential Components of User Interaction

- The "simulated use" as described in your protocol does not include breathing through the device, rather, the user is instructed to "simulate inhaling one cycle of breaths," and to not place their mouth on the device's mouthpiece but to "tell the administrator when you would inhale or exhale". The HF/Usability test, as agreed, should be "simulated" such that no drug is delivered during this phase of testing and drug concentrations are not measured in blood. It is, however, essential that all critical aspects of the interaction between the user and the device that interact with the breath counter and other components be evaluated, and this cannot be done adequately if the user does not actually simulate use by inhaling through the device and interacting with the displayed information consistent with what would occur during actual dosing.

- The dosing process, particularly concerning inhalation through the device and the critical characteristics involved (e.g., depth of inhalation, seal of lips on mouthpiece, etc.), was not described such that the relationship between clinical outcome (dose delivery) and user performance (interaction with the device) is understood and could be evaluated directly in the testing.

  Please modify your protocol to include simulated use that decomposes successful dosing interaction into critical components that can be observed and assessed by a trained observer. The input of clinical expertise regarding specific requirements of user performance will be necessary and your assessors will need to be trained accordingly to enable them to assess essential behaviors. If you have not previously performed an analysis at this level of detail that will be the necessary first step and the results of the analysis should be discussed in your protocol as part of the task analysis and prioritization previously discussed.

2. Training

The protocol needs further clarification on the nature and extent of the training that will be given to test participants and additional rationale for how the training, the lag time between training and testing, and the testing itself will reasonably represent a realistic conditions of the intended users.

3. Screening Participants

- The protocol indicates that participants will not be included unless they are either native English speakers or "highly proficient" with respect to reading and speaking. This appears to be unrealistic and not representative of home users of medical devices. If the intended users for this device are to be "highly proficient" in reading and speaking this requirement should be defined operationally and included in the device labeling.

Please modify the recruiting screener such that it does not systematically exclude representative members of the intended user population, or include an explanation of how only "highly proficient" English readers and speakers are representative or your intended population of users.

4. Testing Procedure

- We are concerned that the stepwise process of device interactions and questioning of test participants as described is artificial and does not allow sufficient naturalistic use.
- It is therefore necessary (see #2 above) that assessors be adequately trained (or possess clinical expertise in this area) to allow them to record essential aspects of interaction including difficulties with use or errors that could impact dosing.

Please modify your protocol such that evaluation will be made on users interacting with the device in a more realistic fashion. Rather than repeated interruptions with questions, users should be allowed to proceed with uninterrupted use of the device while being assessed.

More emphasis should be placed on assessment of performance during use of the device and the questioning held until after the use session is concluded.

5. Data Reduction, Analysis, and Reporting

- The protocol is not specific with respect to how test data will be tabulated or averaged and what is intended with respect to determination of acceptable performance.
- The current description of how data will be reported is vague making it difficult to understand what will be reported and what conclusions might be drawn from it.

The portion of the protocol that describes the test report should address all types of data you plan to collect and how that data will be handled and reported. These are expected to be modified as per the additional analysis and definitions requested above. Note that subjective assessment focused on aspects of use previously identified as critical, are important. Averages of scaled ratings such as overall "ease of use" or "satisfaction" are only of lesser importance.

6. Measures of User Performance and Acceptable Performance Criteria (Pass/Fail Criteria)

- Given the lack of comprehensive assessment of subcomponents of use based and prioritization based on estimated risk (as noted above), meaningful criteria for the measurement of user performance were not included in your draft protocol.

- A variety of types of data are indicated on page 6 of your draft protocol. These are not adequately defined or described. For instance, the current protocol states that "Observed use errors" will be sought but there is no explanation of what these might be or why they are important. Similarly, the nature and relevance of "Task times (stopwatch accuracy)," participant ratings of "ease of use" and responses to interview questions are also unclear. Additionally, you state that testing will be videotaped and that participants will be photographed but you do not explain how video tapes or photographs will be analyzed or used.

Meaningful measures of performance provide a basis for reasonable assessment of the use of a device. Note that you should be testing for the presence of patterns of use error that could compromise safety and effectiveness for this device. Measures need not be taken or reported if their purpose is not relevant and defined. Please provide rationale for all data you intend to collect in your testing with respect to the overall purpose of the test.

7. Modifications to Device Design

The protocol describes a "summative" test which equates to a "validation" of use. Clearly there was no "formative" or "upstream" HF/Usability work on this device. If testing results indicate problematic performance with the device and you address this with some form of mitigation (to include design modification), the resulting modified device will not be considered to have been adequately validated the effectiveness of the modification(s) has been tested.

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

/s/

Dan Brum
6/29/2009 11:25:34 AM
CSO
Signing on behalf of Sugato De and Ron Kaye of CDRH

Dan Brum
6/29/2009 11:25:51 AM
CSO

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 12, 2009
To:	Norman Stockbridge, MD Director, Division of Cardiovascular and Renal Products
Through:	Kellie Taylor, PharmD, MPH, Team Leader Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Judy Park, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Labeling Review
Drug Name(s):	Tyvaso (Treprostinil Sodium) Inhalation Solution 0.6 mg/mL
Application Type/Number:	NDA 22-387
Applicant:	United Therapeutics
OSE RCM #:	2008-1872

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EXECUTIVE SUMMARY

Tyvaso (treprostinil) is a new molecular entity indicated for pulmonary arterial hypertension. The proposed product is delivered by a nebulizer device (Optineb®-ir) which is very complex and may lead errors when administrating the drug. The results of the Label and Labeling Risk Assessment found that the presentation of information on the proposed container label, carton and insert labeling, Patient Labeling, and Instructions for Use, and Human Factors study are vulnerable to confusion and the design/packaging configuration of the device could lead to medication errors. The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and provides recommendations in Section 4.2 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Cardiovascular and Renal Products for assessment of the container label, carton and insert labeling, Patient Labeling, Instructions for Use, and Human Factors study in addition to the packaging configuration for Tyvaso along with Optineb®-ir.

1.2 REGULATORY HISTORY

The Applicant submitted an NDA for Tyvaso (treprostinil) on June 27, 2008. Numerous meetings between the Agency and the Applicant were held to discuss the concerns regarding the inhalation device. The Applicant submitted the foil pouch label, carton labeling, Starter Kit and Refill Kit labeling, and Patient Package Insert on March 12, 2009. The Applicant also submitted the Human Factors study results dated April 8, 2009 and revised Instructions for Use on May 7, 2009.

DMEPA provided labeling comments during the IND phase in 025OSE Review #2007-799.

1.3 PRODUCT INFORMATION

Tyvaso (treprostinil) inhalation solution is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III symptoms. Tyvaso is to be administered by inhalation in four separate treatment sessions per day during waking hours, 4 hours apart. Treatment starts with 1 cycle of 3 breaths (each breath delivers 0.6 mg treprostinil) per treatment session. If 3 breaths are not tolerated, the dose may be reduced to 1 or 2 breaths and subsequently increased. The target dose is 9 breaths per session, as tolerated. Tyvaso is intended for use with Optineb-ir® nebulizer which is an ultrasonic pulsated inhalation device. Tyvaso is available in 2.9 mL clear low density polyethylene (LDPE) ampules containing 1.74 mg treprostinil (0.6 mg treprostinil/mL).

The Starter Kit contains the following:

Contents	Qty
28 ampules (7 foil pouches each containing four ampules)	1
Tyvaso inhalation devices	2
Set of accessory parts (dome assembly, exhalation piece, mouthpiece, and 2 filter shells)	1
Medicine cups	32
Filter membranes	64
Measuring cup	1
Nose clip	1
Plugs for storage between treatment sessions	2
AC wall plug	2
Rechargeable battery	1
12V DC adapter	1
Storage box	1
Carrying case	1

2 METHODS AND MATERIALS

This section consists of two sections which describe the methods and materials used by the medication error prevention staff conducting a label, labeling, and/or packaging risk assessment (see 2.1 Label and Labeling Risk Assessment). The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis (DMEPA) defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication

[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because the medication error prevention staff analyze reported misuse of drugs, we are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. Our Division uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product, the Applicant submitted a Human Factors study on April 8, 2009 for the Optineb®-ir device which is used to administer the drug and we considered the potential for errors associated with device.

The Applicant also submitted the following labels and labeling for the medication error prevention staff review (see Appendices A through D for images):

- Foil Pouch Label (submitted on March 12, 2009)
- Carton Labeling (submitted on March 12, 2009)
- Starter Kit and Refill Kit labeling (submitted on March 12, 2009)
- Patient Package Insert (no image; submitted on March 12, 2009 and revised by the Review Division throughout the current review cycle)
- Prescribing Information (no image; submitted on June 27, 2008 and revised by the Review Division throughout the current review cycle)
- Instructions for Use (no image; submitted on May 7, 2009)

3 RESULTS AND DISCUSSION

3.1 HUMAN FACTORS STUDY

We reviewed the results of the Human Factors study conducted dated April 8, 2009. There were a number of issues identified with the device but few that we considered critical failures. We define a critical failure as one that would lead to inappropriate dose of the medication. We identified the following critical failures noted from the study. b(4)

- Participants' failure to notice two medicine cups – patients would not receive the drug which could lead to underdose or no dose of medication.
- Incorrect installation of baffle plate affecting the particle size distribution. The particle size is important for drug absorption – Some of the drug may not reach the patients' lungs which will result in underdose or no dose of medication

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

- One participant administered 27 breaths instead of 9 due to confusion with the terms of breath vs. cycle of breath vs. treatment session). These dosing errors resulted in overdose

Some other failure modes noted are:

- Overfill of chamber with too much water (one participant filled it up to 90 mL).
- When installing the mouthpiece, it faces the opposite direction
- Filter shells are not securely assembled
- Participants delivered incorrect number of breaths when treatment session was interrupted by power failure
- Participants shut down the device during "00" before the screen displayed "En". The "En" appears 10 seconds after "00."
- There is a possibility of the medicine spilling over in when troubleshooting the device if the dome assembly is not placed upright.

3.2 Label and Labeling Risk Assessment

3.2.1 General Comments for All Labels and Labeling

- The strength should be presented as the total amount of drug per ampule (i.e. 1.74 mg/2.9 mL) followed by the drug concentration (0.6 mg/mL). This presentation is consistent with the other marketed oral inhalation products.
- The light sensitivity statement should also be included on the labels and labeling in addition to the storage statement (i.e. Store the ampules in the foil pack) to make aware the user of the reason for this important instruction.
- The device is referred to as different names in the labels and labeling (e.g. Tyvaso Inhalation System vs. Tyvaso Inhalation Device vs. Optineb®-ir). Since this device is designed to be used only with Tyvaso, it should be referred to as Tyvaso Inhalation Device and not Optineb®-ir.

3.2.2 Foil Pouch Label, Carton Labeling, Starter Kit and Refill Kit Labeling

- The established name should be in parenthesis as this is the usual presentation.
- The dosage and administration statement only instructs patients to see the package insert and not the instructions for use. However, since the Instructions of Use contains vital information for administration of this drug, the dosage and administration statement should also refer to it.
- The inhalation solution will be packaged in low density polyethylene (LDPE) configuration and each foil pouch includes four ampules (4 days supply) which are not individually wrapped. Tyvaso is a light sensitive product therefore not being individually overwrapped can potentially expose the remaining ampules to light. Additionally, the LDPE vials may be separated from the pouch after opening. As

stated in our previous review (OSE Review #2007-799), we are concerned that the packaging of the proposed product in LDPE plastic ampules may lead to confusion. Drug products packaged in LDPE plastic ampules may be more easily confused with one another since few have distinguishing characteristics traditionally utilized on medication containers such as paper labels, color, etc. Although the use of embossed/debossed label information addresses the concern for drug product contamination by the volatile components of the paper label, it also creates an opportunity for medication errors. We have learned through post-marketing reports that the embossed/debossed lettering is difficult to read if not illegible once removed from the foil overwrap. The fact that these vials are difficult to read is a concern that has been voiced by numerous practitioners, patients, and caregivers. In addition, multiple ampules in a single foil wrap lend itself to removal or tearing also affecting the legibility of the foil overwrap itself. Overwrapping each individual ampule may help in maintaining the legibility of the product name and strength.

3.2.3 Patient Insert Labeling

- Instructions of what to do if the patient comes in contact with eyes are absent in the PPI and PI.
- Under "How should I take Tyvaso?" section, it refers to the Patient Instructions for Use at the end of the leaflet but the version submitted for review does not contain Patient Instructions for Use. This information is needed to correctly administer the drug.
- There is no statement discussing the light sensitivity under "How should I store Tyvaso?"

3.2.4 Prescribing Insert Labeling

- The terms and units of dose and strength should be expressed in a consistent manner throughout the labeling to avoid dosing and administration errors. Currently, the strength and dose is expressed in two different units (milligram and microgram). This can cause dosing errors.
- The inconsistent terms used in the insert labeling and Instructions for Use (e.g. [redacted] can cause administration errors which was seen in the Human Factors study. b(4)
- In the Highlights section of Dosage Forms and Strengths, the strength should be presented as total content of drug per ampule (i.e. 1.74 mg/2.9 mL) followed by the drug concentration as this is the usual presentation of other marketed oral inhalation products.
- Under Dosage and Administration, General Dosage Recommendations section, detailed instruction should describe what patients should do if they miss the scheduled session. It is unclear after the patients to resume as soon as possible if the next dose be at least 4 hours apart or return to previous schedule of 4 sessions per day.

- Under Administration, the labeling refers patients to Instructions for Use. Additionally, no specific instructions are given when drug comes in contact with eyes. b(4)
- There is no statement regarding light sensitivity under the Storage and Handling section.

3.2.5 Instructions for Use / Tyvaso Inhalation Device

- The instructional manual is very lengthy consisting of 30 pages.
- Terms used in the insert labeling and Instructions for Use are not consistent b(4)
- Upon following the instructions on screwing the dome assembly onto the device in clockwise direction on page 8, step 2, we note that the mouthpiece can face towards and away from the patient. Additionally, even when the mouthpiece is facing the patient and rotating the inhalation piece (instructed on page 10, step 7), the display screen cannot be seen when using the device. This was confirmed by several participants in the Human Factors study.
- Upon simulating inhaling and exhaling following the directions on page 12, the inhalation indicator light does not always correlate with the length of inhalation. We question what happens if actual inhalation is complete before the end of inhalation indicator light. Does the medicine still go into the lungs?
- The caution section of page 13 states b(4) We feel that these statements are subjective and concerned that patients (especially new patients) may not know what this may be. Additionally, having to troubleshoot the cause of why the medicine is not coming out of the device on page 25 seems impractical especially since there are many possible causes.
- We find that it is impractical to turn the device off and on 3 times per treatment session and counting the breaths downward from 3 to 1 in addition to patients having to log the number of breaths (page 14).
- We question the reasoning for having to store the filter shells, inhalation piece and mouthpiece in upright position in a storage box (p. 17) in between treatment sessions or in a carrying case at the end of day (p. 21). We feel the likelihood of patients following this instruction is unlikely unless there is a good reason of why they should. If so, this should be included in the instructions to alert patients.
- Detailed instructions should be given in what to do if the medicine spills and patients come in contact with the medicine during the cleaning process (p. 20).
- We are concerned about contamination during assembly and disassembly process. The medicine, the distilled water, and the accessory pieces can be contaminated by hand because of the difficulty in assembling and cleaning the parts.

- We note there are four different cleaning/maintaining schedules required for the device (daily, weekly, monthly and every → years) and concerned that this may be difficult for patients to remember. b(4)
- One of the causes of "LH" malfunction signal (page 24) is due to sterile water and the remedy for this malfunction is to add 1 teaspoon of tap water. However, step 1 on page 6 instructs that only to use distilled water. The two instructions are contradictory.
- The device is referred to as different names in the labels and labeling Since this device is designed to be used with only Tyvaso, it should be referred to as Tyvaso Inhalation Device . . Additionally, the drug's proprietary name of the drug (Tyvaso) should be on the device b(4)

The critical failures were discussed with the Applicant on May 22, 2009 meeting. Per the Applicant's letter dated June 5, 2009, the Applicant is proposing to redesign the device post-approval as a Post-Marketing Requirement (PMR). The outstanding issues that remain are listed in Section 4.1.

4 CONCLUSIONS AND RECOMMENDATIONS

The results of the Label and Labeling Risk Assessment found that the presentation of information and design of the proposed container label, carton and insert labeling, packaging configuration of the device and Instructions for Use are vulnerable to confusion that could lead to medication errors. The medication error prevention staff believes some of the risks we have identified can be addressed prior to approval while other risks may require revision post-approval because they relate to device redesign. We provide recommendations in Section 4.2 that aim at reducing the risk of medication errors.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Sean Bradley, OSE project manager, at 301-796-1332.

4.1 COMMENTS TO THE APPLICANT

4.1.1 Requested Changes Prior to Approval

A. General Comments for All Labels and Labeling

1. The strength should be presented as the total amount of drug per ampule (i.e. 1.74 mg/2.9 mL) followed by the drug concentration (0.6 mg/mL) as this is the usual presentation of other marketed oral inhalation products.
2. Include a statement regarding the light sensitivity on the labels and labeling in addition to the storage statement (i.e. Store the ampules in the foil pack) to make the user aware of the reason for this important instruction.

3. The device is referred to as different names in the labels and labeling . Since this device is designed to be used only with Tyvaso, it should be referred to as Tyvaso Inhalation Device . b(4)

B. Foil Pouch Label, Carton Labeling, Starter Kit and Refill Kit Labeling

1. Present the established name in parenthesis as this is the usual presentation.
2. For the Dosage and Administration statement, refer to the Instructions for Use in addition to the package insert since this information is vital in correctly administering the drug (e.g. See package insert and instructions for use for dosage and administration).

C. Patient Insert Labeling

1. Include specific instructions on what to do if drug comes in contact with eyes.
2. "How should I take Tyvaso?" subsection – This subsection refers to the Patient Instructions for Use at the end of the leaflet. Ensure that the Instructions for Use will be included in the back of the PPI.
3. "How should I store Tyvaso?" subsection - Include information in this subsection regarding light sensitivity of the product.

D. Prescribing Insert Labeling

1. Express the strength and dose in the same unit (milligram or microgram) throughout the labeling.
2. Be consistent with the terms used in the insert labeling and Instructions for Use with respect to the description of dosing to avoid dosing errors . b(4)
3. Highlights section of Dosage Forms and Strengths - Present the strength as the total content of drug per ampule (i.e. 1.74 mg/2.9 mL). Place the concentration per mL beneath this statement.
4. Dosage and Administration, General Dosage Recommendations subsection – Provide detailed instructions describing what patients should do if they miss the scheduled session. The labeling instructs patients to resume as soon as possible but does not give further instructions (e.g. should the next dose be at least 4 hours apart or return to previous schedule time of 4 sessions/day?)
5. Dosage and Administration, Administration subsection – The labeling should refer patients to "Instructions for Use" ; for operation of the device. Additionally, include specific instructions on what to do if the drug comes in contact with eyes. b(4)
6. Storage and Handling section – Include information regarding light sensitivity of the product.

E. Instructions for Use

1. Be consistent in the terms used to describe dosing in the insert labeling and Instructions for Use to avoid dosing errors b(4)

2. We question the reasoning for having to store the filter shells, inhalation piece and mouthpiece in an upright position in a storage box (p. 17) in between treatment sessions or in a carrying case at the end of day (p. 21). Patients will not likely follow this instruction unless there is a good reason as to why they should. Please provide the rationale for this instruction to alert the patients or delete this instruction.

3. Detailed instructions should be included in the "End of Day Cleaning of the Accessories" section that clarify what to do if the medicine spills and patients come in contact with the medicine during the cleaning process (p. 20).

4. One of the causes of "LH" malfunction signal (page 24) is due to the use of sterile water. The remedy for this malfunction is to add 1 teaspoon of tap water. However, step 1 on page 6 instructs patients to only use distilled water. These two instructions are contradictory and may confuse the patients. Be clear in the instructions so they do not seem contradictory.

F. Tyvaso Inhalation Device

1. The device is referred to as different names in the labels and labeling (. Since this device is designed to be used with only Tyvaso, it should be referred to as Tyvaso Inhalation Device . Additionally, the drug's proprietary name of the drug (Tyvaso) should be on the device b(4)

4.1.2 Post-Approval Consideration

Per discussion with the Applicant on May 22, 2009 and letter from the Applicant dated June 5, 2009, the Applicant is proposing to redesign the device post-approval as a Post-Marketing Requirement (PMR). We have the following concerns and observations to consider in the redesigning of the device.

A. Human Factors Study

Upon review of the Human Factors study, we find the study acceptable. However, some findings from the study were concerning and should be addressed when redesigning the device.

The critical failures we noted from the study include:

- Participants' failure to notice two medicine cups – patients would not receive the drug which could lead to underdose or no dose of medication.
- Incorrect installation of baffle plate affecting the particle size distribution. The particle size is important for drug absorption – Some of the drug may not reach the patients' lungs which will result in underdose or no dose of medication

- One participant administered 27 breaths instead of 9 due to confusion with the terms of breath vs. cycle of breath vs. treatment session). These dosing errors resulted in overdose

Some other failure modes noted are:

- Overfill of chamber with too much water (one participant filled it up to 90 mL).
- When installing the mouthpiece, it faces the opposite direction
- Filter shells are not securely assembled
- Participants delivered incorrect number of breaths when treatment session was interrupted by power failure
- Participants shut down the device during "00" before the screen displayed "En". The "En" appears 10 seconds after "00."
- There is a possibility of the medicine spilling over in when troubleshooting the device if the dome assembly is not placed upright.

B. Tyvaso Inhalation Device and LDPE Ampules

1. We find that it is impractical for patients to keep track of the number of breaths per treatment session. Patients must turn the device off and on 3 times per treatment session, count the breaths downward from 3 to 1, in addition to patients having to log the number of breaths. Redesigning the device to be able to count up to the maximum breaths per treatment session without having to turn off and on the device should be considered.
2. We note that the mouthpiece can face towards and away from the patient. Additionally, even when the mouthpiece is assembled correctly to face the patient and patients rotate the inhalation piece in 45 degrees according to the Instructions for Use, the display screen cannot be seen when using the device. This was confirmed by several participants in the Human Factors study. Redesign the device or make appropriate interventions to ensure that the patients will be able to correctly install the mouthpiece and see the display screen.
3. The directions on page 12 of Instructions for Use instruct patients to inhale and exhale with the aid of the indication light. However, the inhalation indicator light does not always correlate with the length of inhalation. We question what happens if the inhalation is completed before the inhalation indicator light turns off. We recommend redesigning the device to a breath-actuated inhalation mechanism if possible to reduce the need for coordination.
4. The caution section of page 13 of Instructions for Use states t

b(4)

These statements are subjective and patients (especially new patients) may not know what this may be. We encourage an inclusion of a better description (e.g. taste?).

b(4)

5. If the patients do not — the medicine flowing. They are instructed to troubleshoot the cause of why the medicine is not coming out of the device on page 25 which seems impractical especially since there are many possible causes. Redesign to include a more objective signal that device is not properly flowing and streamline troubleshooting order.
6. If possible, individually overwrap the low density polyethylene (LDPE) ampules since the product is light sensitive and to avoid confusion with other LDPE products in case it becomes separated from the pouch after opening.
7. We are concerned about contamination during assembly and disassembly process. The medicine, the distilled water, and the accessory pieces can be contaminated by hand because of the difficulty in assembling and cleaning the parts. Streamline the design to minimize the frequent need to assemble and dissemble the device.
8. We note there are four different cleaning/maintaining schedules required for the device (daily, weekly, monthly and every –years) and concerned that this may be difficult for patients to remember. Streamline the design to minimize the maintenance of the device.

b(4)

__4__ Page(s) Withheld

_____ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Other Reviews Section-_____

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/s/

Judy Park
6/11/2009 05:32:19 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/12/2009 08:47:27 AM
DRUG SAFETY OFFICE REVIEWER

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: **May 29, 2009**

To: Dan Brum
Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

From: Michael Sauers, Regulatory Review Officer
Zarna Patel, PharmD, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Through: Jialynn Wang, PharmD, Group Leader, DDMAC

Subject: **Drug: Tyvaso (treprostinil) Inhalation Solution**
NDA: 22-387
Comments on draft product labeling (PI) and patient package insert (PPI)

DDMAC has reviewed the proposed product labeling (PI) and patient package insert (PPI) for Tyvaso (treprostinil) Inhalation Solution submitted on March 12, 2009. We also reviewed the comments on the PPI from the Division of Risk Management (DRISK) dated May 19, 2009. We agree with DRISK's comments and offer the following additional comments.

DDMAC's comments are based on the draft label circulated on May 26, 2009.

Highlights

DDMAC recommends removing the word from the third bullet in the Dosage and Administration section for consistency with the PI. (Dosage and Administration 2.1) **b(4)**

In order to prevent minimization of risk in a promotional context, DDMAC recommends presenting the warning relating to Patients with Hepatic or Renal Insufficiency (5.3) in the Warnings and Precautions section of the Highlights, rather than in the Dosage and Administration section.

2.1 General Dosing Instructions

DDMAC recommends including specific instructions regarding how often to adjust the dose of Tyvaso, if known. This section discusses a starting dose and then increasing the dose to 6 breaths per inhalation session, but there is no

information on how much time must elapse prior to increasing the dose or how quickly the increase should be done.

2.3 Patients With Renal Insufficiency

Please consider deleting the statement, This statement may be used in promotion to minimize the risks of Tyvaso treatment in patients with renal insufficiency, since advice recommending caution when treating these patients immediately follows this statement. b(4)

Warnings and Precautions

DDMAC notes that the Remodulin label includes warnings related to General Conditions for Use (5.2) and Abrupt Withdrawal Or Sudden Large Dose Reduction (5.4) that may be relevant when administering inhaled treprostinil. Should these warnings also be included in the Tyvaso label?

5.1 Patients With Pulmonary Disease Or Pulmonary Infections

Please consider including the statement, As this statement is included in the Highlights section of the label, failing to include this statement in the Warnings and Precautions section may minimize the risks of the drug. b(4)

5.2 Risk Of Decrease In Systemic Blood Pressure

The phrase This phrase minimizes the risks of Tyvaso. Please consider revising this sentence to state, b(4)

5.4 Risk Of Bleeding

Please consider revising the statement, "...there **may be** an increased risk of bleeding..." This statement could potentially be used in promotion to minimize the risk of bleeding while on Tyvaso. If the Division confirms that patients are at an increased risk of bleeding when on Tyvaso, please consider revising this statement to, "there **is** an increased risk of bleeding..."

5.5 Effect of Other Drugs on Treprostinil

DDMAC notes that the Drug Interactions section of the PI states, b(4)

Please consider adding this statement to the Warnings and

Precautions section 5.5 for consistency and to prevent minimizing the risks of the drug.

Please consider deleting the phrase,
This statement may be used to minimize the risk of co-administration of Tyvaso with CYP2C8 inducers. b(4)

6.1 Adverse Reactions Identified In Clinical Trials

The adverse reactions displayed in section 6.1 are derived from a study which included patients with NYHA Class IV symptoms. In order to provide contextual information, please consider including a statement such as, "TYVASO is not indicated for patients with NYHA Class IV symptoms."

The most common adverse reactions stated in the first sentence of 6.0 are,
' However, the most common adverse reactions from the TRIUMPH I study are reported as, "cough and throat irritation; headache, gastrointestinal effects, and muscle or bone pain; and syncope." The presentation of two lists of most common adverse events may be confusing and be used in misleading promotion. DDMAC recommends revising these listings to be consistent with one another.

The list of most common adverse reactions from the TRIUMPH I study are reported
The term "gastrointestinal effects" may be used in promotion to minimize the specific risks of the drug. DDMAC recommends listing the specific gastrointestinal effects which patients experienced during clinical trials.

This section presents the statement, "The adverse events during this chronic dosing study were from those obtained in the 12-week placebo controlled trial." Please consider revising the phrase b(4)
as this a vague term and may be used in promotion.

7.2 Anticoagulants

Please see comment regarding Risk Of Bleeding above.

8.4 Pediatric Use

DDMAC notes that the Remodulin label states, "In general, dose selection should be cautious" in this section. We recommend adding this language to this section to prevent potentially misleading advertising.

8.5 Geriatric Use

DDMAC recommends deleting the statement, This statement may minimize the risk of the drug to geriatric patients, given that treatment advice is given regarding these patients immediately following this statement. b(4)

8.7 Patients With Renal Insufficiency

Please consider deleting the statement, This statement may be used in promotion to minimize the risks of Tyvaso treatment in patients with renal insufficiency, since advice recommending caution when treating these patients immediately follows this statement. b(4)

10 Overdose

DDMAC notes that the established name (treprostinil) is used in this section, as well as other sections, instead of the trade name, Tyvaso. This language may be used in promotion to minimize the risks of the product. DDMAC recommends using the trade name of the drug when referring to the product in this section, and others where appropriate, in order to minimize the potential for misleading promotion.

12.2 Pharmacodynamics

This section includes the statement b(4) The terms ' may be used in promotion to minimize risks. DDMAC recommends quantifying these terms if possible.

12.3 Pharmacokinetics

Metabolism

Please consider deleting the word " as it is promotional in tone. b(4)

Renal Insufficiency

Please see comment regarding section 8.7 Patients with Renal Insufficiency above.

14.1 12-Week Placebo Controlled Study In Pulmonary Arterial Hypertension (PAH)

This section states that the primary endpoint in clinical trials is the change in six-minute walk distance (6MWD) at 12 weeks measured at peak exposure, relative to baseline. However, the 6MWD at trough is also described. Does the division feel it is acceptable to use the 6MWD results at trough in promotion? If not, we recommend deleting these statements.

Patient Package Insert (PPI)

What is Tyvaso?

The INDICATIONS AND USAGE section of the draft PI states, b(4)

This qualifies the efficacy of Tyvaso and we would ask for this contextual information in promotional pieces in conjunction with efficacy claims. Please consider adding this information in consumer friendly language to this section.

Thank you for your consult.

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/s/

Michael A Sauers
5/29/2009 03:24:44 PM
DDMAC PROFESSIONAL REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
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Maternal Health Team Review

Date: May 20, 2009 **Date Consulted:** May 1, 2009

From: Jeanine Best, MSN, RN, PNP
Regulatory and Labeling Reviewer, Pediatric and Maternal Health Staff

Through: Karen B. Feibus, M.D.
Medical Team Leader, Pediatric and Maternal Health Staff

Lisa Mathis, M.D.
Associate Director, Pediatric and Maternal Health Staff

To: Division of Cardiovascular and Renal Products (DCRP)

Drug: Tyvaso (treprostinil) Inhalation Solution

Subject: Pregnancy and Nursing Mothers labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of Tyvaso (treprostinil) inhalation solution labeling, NDA 22-387, dated April 30, 2009

Consult Question: Please review the Pregnancy and Nursing Mothers subsections of Tyvaso (treprostinil) Inhalation Solution labeling.

INTRODUCTION

United Therapeutics Corporation submitted a New Drug Application, NDA 22-0837 for Tyvaso (treprostinil) Inhalation Solution on June 26, 2008, for the treatment of pulmonary arterial hypertension (PAH); specifically, for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III symptoms. Treprostinil was initially approved as Remodulin (treprostinil sodium) Injection (continuous intavenous and subcuntaneous routes of injection) on May 21, 2002. Injectable treprositinil has serious safety concerns including the risk of infection with the intravenous route and severe pain that can necesitate administration of narcotics with the subcutaneous route. The inhalation route is not without safety concerns, as irritation effects are noted throughout the respiratory tract and no long-term data is available for tolerability. In addition, the asscoiated nebulizer (OptiNeb) is complicated to use and a new model is under development.

Treprostinil is a prostacyclin analogue. The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation.[1]

No animal reproductive studies have been performed with treprostinil administered via the inhalation route. Segment 1, 2, and 3 studies were performed in rats and rabbits with treprostinil administered via continuous subcutaneous infusion. No developmental toxicity signals were seen with the exception of an increased incidence of fetal skeletal variations (increase in bilateral full rib and right rudimrntary rib on lumbar 1 vertebra) in rabbits associated with maternally toxic doses. No animal lactation studies have been performed with treprostinil.

The Division of Cardiovascular and Renal Products (DCRP) asked the Maternal Health Team (MHT) to review the Pregnancy and Nursing Mothers section of Tyvaso (treprostinil) inhalation solution labeling.

BACKGROUND

Pregnancy and Nursing Mothers Labeling

The Maternal Health Team (MHT) has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The MHT reviewer ensures that the appropriate regulatory language is present and that available information is organized and presented in a clear and useful manner for healthcare practitioners. Animal data in the pregnancy subsection is presented in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human exposure or dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

Pregnancy and Pulmonary Arterial Hypertension

Pregnancy in women with PAH confers a significant maternal mortality rate, regardless of therapy. This mortality rate has decreased to approximately 25% in the past decade, but remains prohibitively high despite advances in PAH therapies and high risk pregnancy management.[2] Females of childbearing potential with PAH should be counseled regarding this risk and encouraged to use

[1] See Draft Tyvaso labeling sent to MHT May 1, 2009

[2] Bedard E, Dimopolous K, Gatzoulis MA. Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? Eur Heart J, 2009 Feb;30(3):256-65

effective contraception. The Proposed Pregnancy and Lactation Labeling Rule contains a section in 8.1 Pregnancy entitled "Clinical Considerations", to provide information and guidance to prescribers, in which one purpose of the section is to discuss describe the risk, if known, to the pregnant woman and the fetus from the disease or condition the drug is indicated to treat and the potential influence of drug treatment on that risk.[3] Under current regulations, the Maternal Health Team has recommended the inclusion of this "Clinical Considerations" section when it helps to clearly communicate important information about the underlying condition being treated or considerations for patient care, and based on the high mortality risk associated with pregnancy in a woman with pulmonary arterial hypertension, a "Clinical Considerations" section of the Pregnancy subsection of labeling may be useful for clinicians.

This review provides MHT's suggested revisions to the sponsor's proposed (with DCRP edits sent to MHT May 1, 2009) Pregnancy and Nursing Mothers subsections of Tyvaso (treprostinil) Inhalation Solution labeling.

SUMBMITTED LABELING
Sponsors Proposed Pregnancy and Nursing Mothers Labeling

b(4)

[3] See Proposed Rule: Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling. FR Vol.73 No.4 Thurs May 29, 2008: 30843-44

b(4)

RECOMMENDATIONS

Provided below are MHT's recommended Tyvaso (treprostinil) inhalation solution labeling for use in pregnancy and nursing mothers. Appendix A of this review provides a track changes version of labeling that highlights the recommended MHT revisions. In, addition, MHT recommends making similar revisions to the pregnancy labeling in Remodulin (treprostinil sodium) Injection.

MHT LABELING RECOMMENDATIONS
HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------

b(4)

MHT Comment:

1. *Although pregnancy information is not required in 'HIGHLIGHTS" for Pregnancy Category B drugs, MHT does not object to the inclusion of this pregnancy information.*

8.1 Pregnancy

b(4)

MHT Comments:

1. *Section reorganized to first provide a short paragraph summarizing the most clinically relevant bottom line based on the available data.*

2. *Required regulatory language for Pregnancy Category "B" products inserted ("Because animal reproduction studies are not always predictive of human response, Tyvaso should be used during pregnancy only if clearly needed.") in place of the draft Pregnancy Category "C" language ("Because animal reproduction studies are not always predictive of human response, treprostinil should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.").*

3. *Recommend Clinical Consideration section as discussed in the Background section of this review.*

b(4)

MHT Comment:

1. *We searched and found no data in PubMed or the LactMed database for information on the use of treprostinil during breastfeeding.*

Appendix A

18 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

6 Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

*Withheld Track Number: Other Reviews Section-*_____

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/s/

Jeanine Best
5/20/2009 12:49:20 PM
LABELING REVIEWER

Karen Feibus
5/20/2009 02:32:13 PM
MEDICAL OFFICER
I agree with the content and recommendations contained in this review.

Lisa Mathis
5/21/2009 03:48:57 PM
MEDICAL OFFICER

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: April 20, 2009

TO: Dan Brum, Regulatory Project Manager
Avi Karkowsky, Medical Officer
Division of Cardio-Renal Drug Products

FROM: Sharon K. Gershon, Pharm.D.
DSI Reviewer
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 22
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-387

APPLICANT: United Therapeutics Corporation

DRUG: Tyvaso (treprostinil sodium, inhaled)

NME: No

THERAPEUTIC CLASSIFICATION: ~~Priority~~ Standard Review

INDICATIONS: treatment of patients with severe pulmonary arterial hypertension

CONSULTATION REQUEST DATE: March 30, 2009

DIVISION ACTION GOAL DATE: April 30, 2009

PDUFA DATE: April 30, 2009

I. BACKGROUND:

TRIUMPH I was an international, multi-center, randomized, placebo-controlled study to assess the safety and efficacy of inhaled trepostinil sodium administered for up to 12 weeks to patients with PAH. Inhaled treprostinil or placebo was added to PAH patients stable on a background regimen of either bosentan (Tracleer) or sildenafil (Revatio, Viagra). Patients were subsequently allowed to enter into an open label continuation phase for long-term assessments of the safety and efficacy of inhaled treprostinil.

The primary efficacy endpoint was change in exercise capacity as measured by 6 minute walk distance (6MWT) evaluated at week 12. Six-minute walk distance as a measure of exercise capacity is routinely utilized in the development of pharmacological treatments for PAH, and is commonly used in clinical practice to assess patient status, disease progression and therapeutic benefit. A peak 6MWT was defined as a walk measured no less than 10 minutes and no more than 60 minutes after study drug inhalation. Other endpoints included Borg dyspnea score, NYHA functional class, PAH signs and symptoms, QOL, disease progression and death.

The protocol inspected was: TRIUMPH 1 STUDY: "Double-Blind Placebo Controlled Clinical Investigation into the Efficacy and Tolerability of Inhaled Treprostinil Sodium in Patients with Severe Pulmonary Arterial Hypertension."

These 2 sites were selected for audit because they were a top enrolling study site for the TRIUMPH 1 study.

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
Vallerie McLaughlin, MD University of Michigan CVC Cardiovascular Medicine 1500 E. Medical Center Drive, SPC 5853/2nd Floor 2372 Ann Arbor, MI	TRIUMPH 1 STUDY 29 subjects	12/9/2008 to 01/07/2009	Pending (DSI Interim: OAI:WL)
Robert Bourge, MD (replaced Raymond Benza as Investigator) University of Alabama at Birmingham Division of Cardiovascular Disease Birmingham, AL	TRIUMPH 1 STUDY 19 subjects	12/15-17, 2008	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending=DSI review of EIR and/or issuance of final post-inspectional correspondence is pending

1.**Vallerie McLaughlin,** MD
University of Michigan
CVC Cardiovascular Medicine
1500 E. Medical Center Drive, SPC 5853/2nd Floor 2372
Ann Arbor, MI 48109-5853

a. What was inspected?
A detailed review of medical records, Informed Consent Documents, study source documents, case report forms and SAE forms were reviewed for 25 (of 30) subjects. Detailed review included that inclusionary criteria were met, all data in the CRFs matched source documents, all data provided by the sponsor matched source documents, Informed Consent Documents (ICD) were accurately documented for each subject, the correct and approved versions of the protocol were used, and that protocol procedures were followed for each subject throughout the study. In addition, documentation of protocol deviations and adverse events was reviewed in detail, as well as drug accountability records. The inspection performed a limited review for 5 (of 30 records) with respect to eligibility criteria, line listing data, ICD, dosing and AE/SAE reporting. The inspection reported that 14 subjects received placebo and 15 subjects received the active agent Treprostinil.

b. General observations/commentary: A 5-observational FDA-483 was issued to Dr. McLauglin. Observations included: 1) not conducting the investigation according to the investigational plan [21 CFR 312.60]; 2) failure to maintain accurate case histories [21 CFR 312.62(b); 3) failure to report all AEs to the sponsor [21 CFR 312.64]; 4) failure to promptly report SAEs to the IRB [21 CFR 312.66]; 5) failure to maintain accurate drug disposition records [21 CFR 312.62(a)].

Item 1) The most significant finding reported was that 49 of 131 (~38%) 6-MWT performed during the double-blind study, were done outside the protocol specified timeframes, with respect to peak and trough times. Please see the attached tables at the end of this CIS that provide the specific deviations.

During the open label portion of the study, 6MWTs were similarly not completed within protocol-required timeframes. A total of 16 of 72 walk tests were not performed correctly during the open-label portion. Twelve (12) of these walk tests were not performed at peak tresprostinil levels (10-60 minutes post inhalation at Visits 2, 3 & 4), and 4 were not completed within peak bosentan or sildenafil times. These time discrepancies ranged between 0.5 hours to as long as 9. 3 hours. It is significant to note that none of these protocol deviations had been reported to the IRB. Furthermore, the inspection observed that 6-MWTs were continuously performed outside the required timeframe, even though it was repeatedly requested by study monitors that Dr. McLaughlin ensure all six-minute walks tests be performed within the protocol

required window. There was no documentation (no phone calls or other communications documented) reporting if subjects were reminded of visits or timeframes, or that walk technicians were not running on schedule. The protocol states that noncompliance for any reason, including inability or unwillingness to take drug at required times prior to walk test completion, was grounds for removal of any subject from the study. DSI believes the failure to administer these 6-MWTs within the required timeframes would impact the primary endpoint for this study.

In addition, the investigation found instances where pregnancy tests and vital signs were not performed, as per protocol. One subject of child-bearing potential (13011) did not have a pregnancy test at Visit 1 or at Visit 3; and several subjects did not have vitals measured at Visits 4 and 5.

Item 2) Another significant finding was that the inspection noted many discrepancies between data that was documented in the source records and data documented on the CRF, with respect to timings between drug administration and 6-MWT times. These time differences might be significant in terms of the primary efficacy evaluation. For example,

- For Subject 13010, for Visit 1, the CRF documents that bosentan was administered 4.17 hours before the 6-MWT, whereas the source record documents 3.67 hours.
- For Subject 13005, at Visit 3, the CRF documents the 6-MWT was administered 26.83 since last bosentan dose, whereas the source document reports 14.83 hours.
- For Subject 13006, at Visit 1, the CRF reports an increase in oxygen use during the 6-MWT, whereas the source documents report no increase in oxygen use.

The inspection reports 19 examples of these sorts of discrepancies. The investigation also reported that data was altered in case histories using white-out, and provided 20 examples of this deficiency for records reviewed. Some examples were: 'white- out of answer to question 9 of exclusion criteria on eligibility checklist' for Subject 13018, 'white-out of SAE onset date of 1/12/2006' and white-out of information, and type-over with syncope on the SAE form' for Subject 13008. The white-outs do not represent alterations to the data and DSI does not believe they affect the efficacy evaluations.

Item 3) The inspection identified 6 adverse events found in clinic notes and/or physician histories and physicals that were not reported to the sponsor. These included:

- fall and ankle sprain in Subject 13006 that occurred on 12/21/2005;
- dyspnea and chest pain in Subject 13020, for which the investigator became aware of on 01/09/2007, but did not report to the sponsor;
- increased dyspnea in Subject 13025 on 11/12/2007;
- difficulty sleeping in Subject 13025 on 11/19/2007; and
- lightheadedness in Subject 13028 on 08/01/2007.

With respect to failure to report all SAEs to the sponsor, the investigation reported that Subject 13008 had a SAE of syncope which required treatment in the ER of a local hospital ——— . The investigator was notified of this event on 12/5/2005. This event was not reported to the sponsor. However, a second event of syncope occurred in this same subject on 12/4 – 5/2005. This event was reported to the sponsor. Because the event occurred in more serious form the second time, and the second event was reported to the sponsor, DSI does not consider this to be a significant violation for this one subject. b(6)

Item 4)
In addition the inspection identified numerous instances where SAEs and AEs were not reported to the IRB.

- There were 8 instances in which SAEs were not reported to the IRB, and 2 instances where an SAE was reported late. For example, Subject 13017 had hemoptysis beginning on 5/17/2007, but the AE was not reported until 07/16/2007, almost 2 months later.
- There were at least 69 adverse events, involving 18 of 29 subjects, that were not reported to the IRB. Examples included sore throat to Subject 13005 on 12/27/2005, mouth sores to Subject 13006 on 11/07/2005; and sore throat to Subject 13009 on 05/05/2006.

Note that other than the AEs identified in Item 3) that were not reported to the sponsor, the SAEs and AEs that were not reported to the IRB, were, however, reported to the sponsor.

Item 5)
With respect to study drug accountability, the inspection reported 17 discrepancies between the number of study kits returned to the pharmacy (by subjects), and the number of kits returned to the sponsor. For example, for Subject 13019, 7 kits were documented returned to — pharmacy by the subject, whereas 2 kits were documented as returned by — pharmacy to the sponsor. The inspection did not find inaccuracies with respect to actual drug dispensation to subjects. It appears that subjects did, in fact, received the correct drug, according to their treatment assignment. b(6)

Dr. McLaughlin provided a written response to the observational findings, in a letter dated February 18, 2009. Her responses promised corrective action, but do not negate the significance of the findings.

c. Assessment of data integrity: The significant issues noted during the inspection were that ~ 38% of the 6-MWTs were performed outside the protocol required timeframes, with respect to drug administration times (see attached Table from EIR) and there were several discrepancies between the documentation of the 6-MWT measures on source records as compared to CRFs. DSI believes that these findings are significant to evaluation of the primary efficacy measurement for this study, and does not consider the data pertinent to the 6-MWT reliable in support of efficacy based on inspectional findings; however, DSI would recommend the review division see the attached tables following the CIS, which provide the exact details

of the deviation from the 6-MWT with respect to dosing of drug, and consider this in their assessment of efficacy. Note that these results were previously provided to the medical officer in the review division in consideration of efficacy assessment. Although there were several AEs and SAEs that were not reported to the IRB for this study, with the exception of the five outlined above in Item 3), these were reported to the sponsor. There were no other significant deficiencies with respect to safety assessment, and as such, DSI recommends that the safety data from this study can be used in support of the NDA, although DSI recommends that the review division consider 5 AEs that were not reported to the sponsor in their assessment of the safety outcome.

Due to the numerous issues identified at this site with respect to efficacy data integrity and human subject protection, DSI is recommending a WL be issued to Dr. McLaughlin.

2.**Robert Bourge,** MD (replaced Raymond Benza as Investigator)
University of Alabama at Birmingham
Division of Cardiovascular Disease
311 THT, 1900 University Boulevard
Birmingham, AL 35294-0006

a. What was inspected: Twenty subjects were screened at this site, and 19 subjects were enrolled. At the time of the inspection, 9 subjects were still active, and being followed in the open-label phase. All 20 subjects' Case Report Forms and medical charts/source records were reviewed during the inspection. Signed written informed consents were observed for all 20 subjects, drug accountability records were reviewed. and the consents were noted as signed prior to all study procedures.

b. General observations/commentary: Records were well organized, allowing for ease in review. Source records documented that all subjects met eligibility criteria (with exception of 2 sponsor waivers that allowed subject entry into the study). No discrepancies were noted between source records and CRFs. Primary efficacy endpoints were verified and consistent between sponsor-provided data listings and source records. No instances of unreported adverse events, protocol deviations, concomitant medications or intercurrent illnesses were observed. All subjects signed informed consent documents prior to initiation of study procedures.

Drug accountability records were audited and no discrepancies were noted.
Review of subject records documented appropriate dosing regimens; dosage adjustments were made by the PI as needed based on the subject's ability to tolerate the dose. The 6-MWT was conducted in the Cardiology Clinic on a track marked in meters. The site followed the standard recommended walk test procedure included as Attachment IV to the protocol. No FDA-483 was issued during the inspection.

c. Assessment of data integrity: With respect to the 6-MWT, the inspection did not identify any major issues concerning drug administration times. Adverse events appeared as accurately reported. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two sites were inspected as part of a data audit in evaluation of this NDA. Several discrepancies were identified at Dr. McLaughlin's site that question the 6-MWT and their contribution to the impact of efficacy determination, and as such DSI does not consider this data reliable in support of the application. However, DSI defers the evaluation of the 6-MWT findings and their impact on final efficacy outcome to the review division. DSI considers the safety data to be reliable, and to recommends that the 5 AEs that were not reported to the sponsor, be considered in assessement of the safety outcome.

The audit found that Dr. Bourge appears to have conducted the study adequately, and DSI considers data from this reliable in support of the NDA.

{See appended electronic signature page}

Sharon K. Gershon, Pharm.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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Division of Scientific Investigations

Subject ID/ Initials	Visit	Required Time of Administration	Actual Time of Administration	Time Difference
Treprostinil				
13001/	V5	After or ≥4 hours before walk test (trough)	1.5 hours before walk test	2.5 hours
13006/	OLV5	10-60 minutes before walk test (peak)	2.58 hours before walk test	1.58 hours
13009/	OLV4	10-60 minutes before walk test (peak)	2.08 hours before walk test	1.08 hours
13011/	V5	After or ≥4 hours before walk test (trough)	3.47 hours before walk test	.53 hours (~32 minutes)
13013/	V5	After or ≥4 hours before walk test (trough)	3.47 hours before walk test	.53 hours
13024/	V5	After or ≥4 hours before walk test (trough)	2.75 hours before walk test	1.25 hours
13027/	V5	After or ≥4 hours before walk test (trough)	2.75 hours before walk test	1.25 hours
13027/	OLV3	10-60 minutes before walk test (peak)	3.25 hours before walk test	2.25 hours
Bosentan				
13005/	V3	3-5 hours before walk test (peak)	14.83 hours before walk test	9.83 hours
13009/	V2	3-5 hours before walk test (peak)	5.83 hours before walk test	.83 hours (~50 minutes)
13017/	V1	3-5 hours before walk test (peak)	6.37 hours before walk test	1.37 hours (~1 hour 22 minutes)
13017/	V3	3-5 hours before walk test (peak)	8.67 hours before walk test	3.67 hours
13020/	V1	3-5 hours before walk test (peak)	5.53 hours before walk test	.53 hours

b(6)

Sildenafil				
13016/	V1	30-120 minutes before walk test (peak)	4.33 hours before walk test	2.33 hours
13016/	V3	30-120 minutes before walk test (peak)	3.50 hours before walk test	1.5 hours
13021/	V2	30-120 minutes before walk test (peak)	4.42 hours before walk test	2.42 hours
13022/	V1	30-120 minutes before walk test (peak)	6.25 hours before walk test	4.25 hours
13024/	V34	30-120 minutes before walk test (peak)	5.5 hours before walk test	3.5 hours
13027/	V1	30-120 minutes before walk test (peak)	4.17 hours before walk test	2.17 hours

b(6)

In addition, study protocol required that during the Open Label portion of the study, a "peak 6MWT will occur", in reference to the investigational drug (Treprostinil). Of 72 walk tests completed during the open label study, 12 were not completed at peak of investigational drug, for example:

Subject ID/ Initials	Visit	Required Time of Administration	Actual Time of Administration	Time Difference
13006/	OLV5	10-60 minutes before walk test	2.58 hours before walk test	1.58 hours
13009/	OLV4	10-60 minutes before walk test	2.08 hours before walk test	1.08 hours
13029/	OLV2	10-60 minutes before walk test	3.25 hours before walk test	2.25 hours

b(6)

Further, the protocol stipulates that "All 6 minutes walks should be performed 3-5 hours after the bosentan dose or 30-120 minutes after the sildenafil dose." An additional 4 walk tests were not completed within this timeframe during the open label portion of the study.

Subject ID/ Initials	Visit	Required Time of Administration	Actual Time of Administration	Time Difference
Bosentan				
13014/	OLV2	3-5 hours before walk test	5.17 hours before walk test	.17 hours
13017/	OLV4	3-5 hours before walk test	5.5 hours before walk test	.5 hours
Sildenafil				
13023/	OLV2	30-120 minutes before walk test	3.25 hours before walk test	1.25 hours
13027	OLV4	30-120 minutes before walk test	.25 hours before walk test	.15 hours

b(6)

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/s/

Sharon Gershon
4/23/2009 01:49:07 PM
CSO

Tejashri Purohit-Sheth
4/23/2009 04:44:34 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Office of Device Evaluation
9200 Corporate Boulevard
Rockville, MD 20850

NDA 22-387 – Regulatory Device Consult

Date: April 1, 2009
To: The Record
From: Sugato De, Biomedical Engineer
Applicant: United Therapeutics Corporation
Device Name: Optineb-IR Ultrasonic Nebulizer (Tyvaso Inhalation Solution)

Office: HFZ-480
Division: DAGID/ARDB

A. Purpose and Submission Summary

In NDA 22-387, United Therapeutics Corporation has proposed a novel combination product intended for the delivery of treprostinil sodium (Tyvaso®) to patients with pulmonary arterial hypertension (PAH). Tyvaso is administered in a home-care setting to patients using the Optineb-IR Ultrasonic Nebulizer, manufactured by NebuTec.

Within the context of this regulatory consult, the capacity of the Optineb-IR nebulizer to adequately deliver the specified dose of aerosolized medication will be reviewed in detail. In addition, relevant test reports concerning biocompatibility, electrical safety, electromagnetic compatibility, and software validation are examined to evaluate the safety and efficacy of the proposed device.

As is further detailed below, following the resolution of several concerns regarding the particle size distribution analysis, biocompatibility test reports and electrical safety tests in the supplement submitted by the sponsor on January 2, 2009, the sole remaining device-related concerns relate the usability of the Optineb-IR ultrasonic nebulizer in the home environment. Specifically, in a letter dated March 5, 2009, the Agency communicated a concern to the sponsor that the current design of the device and the materials supporting its use (e.g. user manual) could possibly induce or allow use-errors that may compromise the user's ability to deliver medication properly and could thereby pose significant risks. Among the major concerns identified by the Agency was whether users can properly dose themselves with a total of nine breaths using the currently designed breath counter mechanism. This counter counts only up to three and the patient must restart the device two additional times to receive the required nine breaths. As of April 1, 2009, the sponsor has not performed a comprehensive Usability Analysis incorporating the evaluation and prioritization of user-related risk. Following this evaluation, it has been recommended that the sponsor perform a Human Factors Study demonstrating the safe simulated-use of the Optineb-IR device in an environment that approximates the intended home-care setting. The purpose of this study is to evaluate the severity of the risks anticipated in the initial Usability Analysis, and to identify user-related risks that may have been unanticipated by the sponsor. In the end stages of the study, the sponsor should propose adequate mitigation measures for the identified user-related risks, and may be expected to modify and revalidate the proposed device as necessary to alleviate safety-related concerns regarding its use.

Recommendation: The combined drug/device delivery system is not approvable without a comprehensive Usability Analysis and Human Factors Study as described above. Additionally, it has been recommended that the sponsor perform an abbreviated clinical study demonstrating that patients are able to inhale the prescribed dose of medication. As this clinical study is expected to be performed in a reasonably approximated environment of use, the Human Factors Study should be performed first and all user-related risks should be adequately mitigated.

B. Device Description

	Yes	No	N/A
Is the device life-supporting or life sustaining?		X	
Is the device an implant (implanted longer than 30 days)?		X	
Does the device design use software?	X		
Is the device sterile?		X	
Is the device reusable (not reprocessed single use)? Are "cleaning" instructions included for the end user?	X		

The Optineb®-IR Nebulizer is a device intended for single patient use in the administration of inhaled treprostinil. The nebulizer operates ultrasonically by energizing a piezoelectric transducer at 2.4 MHz. This action collimates distilled water stored in the water reservoir, thus energizing liquid medicine stored in the medicine cup and creating an aerosolized cloud of medication to be delivered to the patient. The dome and baffle components of the nebulizer are designed to control the size of the particles that are emitted from the device. The nebulizer's software responds by providing visual and audible signals to the patient synchronizing the patient's breathing with the nebulization process. The Optineb-IR performs this operation for three consecutive cycles, and dispenses the prescribed dosage at a specified particle size.

The Optineb®-IR consists of a low voltag[redacted] electronic control unit, plastic nebulizer components which are reusable for up to [redacted] days, daily disposable medicine cups, and daily disposable inhalation and exhalation filter media. b(4)

The Optineb®-IR may be powered by one of three methods:

- A TUV Recognized component (IEC60601-1 & EN60601-1-2) [redacted] VAC power supply, or
- A rechargeable battery pack that my be used in conjunction with the aforementioned power supply, or
- A 12VDC automobile (cigarette lighter) adapter.

Treprostinil (15AU81, UT-15) is a stable tricyclic benzindene analogue of the naturally occurring prostacyclin, PGI2 (epoprostenol), a member of the eicanosoid family of autocoids; these compounds occur widely in tissues and have important pharmacological properties with potent activity, especially on the cardiovascular system and smooth muscle. Tyvaso® (treprostinil sodium) Inhalation Solution, 0.6 mg/mL, has been developed as a treatment for pulmonary arterial hypertension (PAH), an orphan disease with a global prevalence of approximately 50,000-100,000 patients.

The recommended dose of Tyvaso is up to nine breaths (54 micrograms) per administration and up to 4 administrations per day; i.e., up to 36 breaths per day, with a maximum dose of twelve breaths (72 micrograms) per administration. The maximum theoretical aerosol concentration of nebulized treprostinil in Tyvaso is [redacted], although the actual aerosol concentration is considerably lower. b(4)

Reviewer's Note: The Optineb-IR device is not a general-purpose nebulizer, and is intended exclusively for use with treprostinil inhaled solution. The sponsor has not submitted a separate 510(k) Premarkent Notification for the device, and all device-related information is included in the context of IND 70,362 and NDA 22-387. As such, the device is not currently cleared for any intended use in the United States, and the current submission is solely attempting to validate its use with Tyvaso Inhalation Solution.

C. Labeling

A summary of the labeling information for the Tyvaso Inhalation Solution was provided for review in NDA 22-387. The information is provided in the form of a User's Manual, in which the device is described in detail, including specifications, components and optional accessories.

Comprehensive instructions are given regarding how to assemble the nebulizer, how to connect the nebulizer to the power supply, how to fill the medication, and how to operate the nebulizer.

Cleaning instructions are provided for the nebulizer chamber lid, continuous filling equipment, nebulization chamber and the mouthpiece of the device. For each part, cleaning, disinfection, and machine washing instructions are provided. Troubleshooting information for various faults is included in the manual, including possible causes and remedies. Problems covered include insufficient nebulization, failures in the power indicator on the face of the device, nebulizer shut-off, and overflow of medication from the medication cup.

Electrical emissions and immunity information are also provided, and will be discussed in further detail.

Reviewer's Note: In the initial review of the supplied User's Manual, the Agency concluded that the assembly and usage instructions given would be too difficult for patients and users of the device to comprehend. Additionally, the manual in its present form does not include any information about the drug, including its indications for use, side effects, etc.

In lieu of the OPTINEB-IR device user manual that you have proposed, the Agency recommends that the sponsor instead submit (1) a Patient Package Insert (PPI) and (2) Instructions For Use (IFU). The PPI is intended to focus primarily on the drug product itself, whereas the IFU would focus on the device. PPIs are intended to enhance appropriate use of medications and provide important risk information to patients; the information should be consistent with the information presented in the full prescribing information. IFUs are intended to support the appropriate use of your device.

The following sections with diagrams should be considered for inclusion:

- "Preparing For Your Treatment",
- "Using your OPTINEB-IR",
- "Maintenance & Cleaning"

This information was communicated to the sponsor in the March 5, 2009 IR Letter, and United Therapeutics has indicated that the suggested material would be provided for review. However, the following device-related considerations remain in regards to the labeling.

- Because the Optineb-IR is intended solely for delivering inhaled treprostinil, and has not been approved to deliver any other drug product, CDRH believes that a standalone device Instructions for Use (IFU) is not necessary for the device. Instead, a comprehensive User's Manual should detail the use of the Optineb-IR in delivering treprostinil. Included in this manual should be the specific instructions for the assembly of the device, the use of the device in delivering the prescribed dosage of drug, and relevant cleaning and maintenance information.
- A complete range of drug and device specifications should be presented in the User's Manual in tabular form. These would include, but are not limited to, the prescribed dosage specifications in terms of micrograms of drug, the mass median aerodynamic diameter (MMAD) of the delivered drug, the geometric standard deviation of the MMAD and the percent of drug dose delivered which falls in the respirable fraction (i.e. [redacted] s). These specifications are intended to provide both the caregiver and the patient with an accurate representation of the dosage capacities of the integrated combination product. b(4)

D. Sterilization/Shelf Life/Reuse

No component of the subject device is provided sterile.

The device is intended to be single-patient use, and contains plastic nebulizer components which are reusable for up to days, daily disposable medicine cups, and daily disposable inhalation and exhalation filter media. b(4)

E. Biocompatibility

Potential device-related effects were evaluated in a program of biocompatibility studies with extracts of the nebulizer materials that come in contact with the drug. The testing program was determined by reference to ISO 10993.

There are three different materials of construction in the ventilatory pathway, as shown below.

Device Components in the Ventilatory Pathway

Device Part	Material of Construction
Medicine Cup	
Sealing O-Ring	
Remaining Parts	

b(4)

The study materials were provided for testing. The studies and study references are listed in the table below.

Biocompatibility Studies* with Nebulizer Components

Study Type	Study Reference
Extracts of APEC 1745 Plastic	
In vitro cytotoxicity	Report #423422
Intracutaneous reactivity in rabbits	Report #423418
Sensitization in guinea pigs	Report #423423
Genotoxicity by Ames Test	
Genotoxicity by Chromosomal Aberration	Ongoing
Genotoxicity by mouse lymphoma	Ongoing
Implantation	Bayer
Subchronic toxicity study in mice	Ongoing
Extracts of O-Ring and Medicine Cup	
In vitro cytotoxicity	Report #423422
Intracutaneous reactivity in rabbits	Report #423418
Sensitization in guinea pigs	Report #423423
Genotoxicity by Ames Test	Ongoing
Genotoxicity by Chromosomal Aberration	Ongoing
Genotoxicity by mouse lymphoma	Ongoing
Implantation	Ongoing

b(4)

The required testing was determined per ISO 10993 for Tissue/Bone/Dentin communicating, chronic exposure devices. This testing includes cytotoxicity, intracutaneous reactivity, sensitization, genotoxicity, and implantation on all device parts in the ventilatory pathway.

Since the mouthpiece comes into direct contact with the patient, this part requires sub-chronic toxicity and intracutaneous reactivity (irritation) testing as well. The results of the testing and the status of ongoing testing are discussed below.

Cytotoxicity

The MEM Elution test was designed to determine the cytotoxicity of extractable substances. An extract of the sample was added to cell monolayers and incubated. The cell monolayers were examined and scored based on the degree of cellular destruction. The samples are scored against a set of controls on a scale of 0 – 4. The sample meets USP requirements if all results are Grade 2 or less.

All the tested components met the requirement.

Intracutaneous Reactivity (Irritation)

The Intracutaneous Reactivity test was designed to determine if any chemicals that may leach or be extracted from the test article were capable of causing local irritation in the dermal tissues of rabbits. The device components were extracted per protocol against saline solution and cottonseed oil. The resulting extracts were then used for testing. All of the device components in both extracts met the ISO 10993-1 requirements.

Sensitization

This test is designed to evaluate the allergenic potential or sensitizing capacity of a test article. Extracts of the test material are tested as potential contact allergens in guinea pigs. All of the device component materials specified in the table above met the ISO 10993-1 requirements.

Implantation

The purpose of this study is to evaluate the local effects of a test article in direct contact with living skeletal muscle tissue. Implantation studies were performed by the manufacturer of the component, . The material met the ISO 10993 requirements.

Implantation testing is complete for the material but is still in progress for the remaining two components, which are the medicine cup and sealing ring

b(4)

Genotoxicity

This test is designed to evaluate potential genetic effects of the test articles. Ames mutagenicity testing was performed by the manufacturer of the component, . The material met the ISO 10993 requirements for this test.

b(4)

Ames mutagenicity testing is complete for the material (as noted above) but is still in progress for the remaining two components, which are the medicine cup and sealing ring . Mouse lymphoma testing and chromosomal aberration testing are in progress for all three components.

Sub-Chronic Toxicity

The purpose of this study is to evaluate the systemic toxicity of leachable compounds from the test article. This test is intended for medical devices with a contact duration categorized as permanent (greater than 30 days). This testing is required only for the mouthpiece, which is —— material and is in progress. b(4)

Reviewer's Note: While all protocols and acceptance criteria provided by the sponsor are adequate in reference to ISO 10993-1, completed test reports are required for review for each of the tests specified above. The tests that the sponsor has indicated are currently ongoing should be completed to justify the biocompatibility requirements for the Obtineb-IR Ultrasonic Nebulizer.

F. Software

Version: OPTI-SMD-0708 Ver 7.2008		
Level of Concern: Moderate		
	Yes	**No**
Software description:	X	
Device Hazard Analysis:	X (Incomplete.)	
Software Requirements Specifications:	X	
Architecture Design Chart:	X	
Design Specifications:	X	
Traceability Analysis/Matrix:	X	
Development:	X	
Verification & Validation Testing:	X	
Revision Level History:	X	
Unresolved anomalies:	X	

Validation and verification activities cover the testing of the general specifications of the device, and test all relevant indicators for power, medication and device failures. All user-interface prompts are tested according to specifications. The report is separated into customer requirements tests, functional tests, service tests, production tests, risk analysis tests, standards tests and environmental tests.

→*Level of Concern:* In accordance with the FDA guidance "Content of Premarket Submissions for Software Contained in Medical Devices," the software level of concern for the new device has been determined as "moderate" because the failure of the device software may cause non-serious injury to a patient. A possible overdosage of treprostinil due to the failure of the breath counter mechanism may lead to such side effects as headache, jaw pain and other similarly minor symptoms

→*Software Description:* In this section, the sponsor gives a summarized introduction to the software features of the Optineb-IR. This software interfaces to the user through a simple hardware interface consisting of the following components.

- ON/OFF Push Button
- A push button for therapy Start/Stop
- Dual segment display for low H_20, Low Voltage, Breath Countdown, and End of Therapy Status.
- Multicolored LED used for operation, standby and "attention needed" status indication.
- Green LED that is used to instruct the patient to being drawing a breath.
- Sonic beep transducer as a simple audible sonic aid during operation.
- Water Level OK Indicator (OK/Not OK) & Input Power Voltage OK Sense (OK/Not OK)

Program Flow:

After switching on the OPTINEB@-IR, the number "03" will be displayed. The number indicates three cycles of the AICI (Active Intermittent Controlled Inhalation) mode. After pressing the "Start/Stop" button, two short acoustic signals are rendered by the device in order to instruct the patient to begin the exhalation process. The exhalation will be accompanied by a three second lasting acoustic signal. Simultaneously an aerosol will be produced (HF amplifier will be activated).

After three sec the ultra bright LED will light up to require the inhalation process. The numbers displayed on the front of the display will count down from "03" to "02", which is the number of the remaining inhalation-cycles. The LED flashes in ½ sec intervals and finishes after five seconds. After the LED light powers off, the device remains silent without any action for five seconds. The patient normally uses this break to exhale and to recover.

The process described above will be repeated three times as the each inhalation cycle of the device requires the user to inhale a total of three times. After the third breath "En" will be displayed on the front of the device and an acoustic signal will resound.

The current design of the device requires the patient to complete a total of three inhalation cycles in order to deliver nine breaths during each treatment. This requires the user to power the device off and on between each inhalation cycle.

→ *Device Hazard Analysis:* A risk analysis for the software of the Optineb-IR has been provided for review by the sponsor. Standards referenced in order to satisfy this documentation requirement include IEC 62304 and ISO 14971. While this analysis includes only risks related to software failure modes, the recommended usability risk analysis should include risks related to the use of the device. Therefore, potential risks may remain that require the device to be modified as necessary.

→ *Software Requirements Specification:* A Software Requirement Specification was written to include the functional, performance, interface, design and developmental requirements from the Optineb-IR System Specification. All identified hazards have been mitigated to the SRS and have been tested at the software system verification and software validation levels.

→ *Architecture Design Chart:* An overview of the Optineb-IR and its interface with compatible components is provided in the Architecture Design Chart.

→ *Traceability Analysis:* In this document, software requirements specifications and software verification activities are traced to the Optineb-IR Validation and Verification Report.

→ *Software Development:* As previously mentioned, the Optineb-IRB Software Development was performed in accordance with IEC 62304: Medical Device Software Life Cycle Processes. Internal design control procedures incorporated the standard were followed and provided the disciplined processes for planning, design, verification, validation and design reviews for software development.

→ *Verification and Validation Documentation:* A description of all validation and verification activities at the unit, integration and system level are given in this section. System level test protocols, including pass/fail criteria and test results are also provided. Validation tests for each performance specification provided in the labeling, and tests to confirm that all device accessories are compatible with the system software, are provided.

→ *Revision Level History:* A revision history log, documenting all major changes to the software during its development life cycle, is provided for review. The sponsor states that this is the first release of the Optineb-IR Software in the United States , and that the release version number is Ver 7.2008.

→ *Unresolved Anomalies:* No anomalies affecting safety and efficacy have been identified at the time of releasing the current software version.

G. Electromagnetic Compatibility and Electrical, Mechanical and Thermal Safety

It is stated in the submission that the device will be certified to the following international standards:

IEC 60601-1: Medical Electrical Equipment – Part 1: General Requirements for Safety
IEC 60601-1-2: 2001, Medical Electrical Equipment – Electromagnetic Compatibility

As described below, all relevant emissions and immunity tests were completed, and the protocols, pass/fail criteria, results and conclusions were included with each test. The electrical safety and mechanical tests have also been performed, and are seen in Section 12.7.14.

Electrical Safety:	
Battery Power	Pass
Electrical Power Indicators	Pass
Overcurrent Protection	Pass
Dielectric Withstand	Pass
AC Power Grounding & Polarity	Pass
Leakage Current	Pass
Electromagnetic Compatibility:	
Emissions	
Radiated (30, 37 db/uV at 10/30 m)	Pass
Conducted	Pass
Magnetic Fields	Pass
Immunity	
ESD (± 2,4,6 kV contact, ±2,4,6,8 kV air)	Pass
Radiated Electromagnetic Fields (3 V/m)	Pass
Steady-State Voltage	Pass
Dropout	Pass
Slow Sags & Surges	Pass
Fast Transient Bursts	Pass
Fast Surges	N/A
Conducted Electromagnetic Energy	N/A
Magnetic Fields	Pass.

Mechanical:

Shock	Pass.
Sinusoidal Vibration	Pass
Random Vibration, Wide band	Pass
Fluid Spill Resistance	Pass
High & Low Temp & Humidity	Pass
Surface Temperature	Pass

H. Performance Testing – Bench

Nonclinical laboratory testing was performed on the Optineb-IR Ultrasonic Nebulizer to demonstrate the safety and effectiveness of the device in delivering a specified dosage of inhaled treprostinil to a patient. The key elements in measuring the performance of the device were the total quantity of drug delivered, mass median aerodynamic diameter, geometric standard deviation, respirable fraction, respirable dose and treatment time.

Total Nebulizer Output

This study was an attempt to characterize nebulizer output and to analyze the output in terms of total dose delivered during each breath. Using an Anderson Cascade Impactor, successive cycles of three breath outputs were collected to simulate a total of twelve breaths. This procedure was repeated using several Optineb-IR nebulizers, and four times for each individual nebulizer. In a representative nebulizer, for each cycle of three breaths, the sponsor measured a total dose output of 16.3, 17.1, 18.2, and 17.8 μg. Across all nebulizer samples, RSDs were above 15% for each three breath cycle, thus suggesting the variability observed in the early dose output studies cited by the sponsor was still present. However, these results were not significantly different from one another and suggest that a single breath output was just under six micrograms. In total, total outputs of treprostinil over each nine breaths ranged from 47.8 - 57.0 μg. As such, the sponsor's specified dosage of 54 micrograms of drug over nine inhalations has been validated from a device perspective.

Particle Size Distribution Analysis

The sponsor has provided a test report detailing results obtained from the evaluation of the Optineb-IR Nebulizer by determining particle size distribution by cascade impaction analyzed by HPLC for treprostinil drug products.

A total of three Optineb-IR nebulizers were evaluated for particle size by cascade impaction using nine breaths at five time intervals. The time intervals evaluated were initial, four hours, eight hours, twelve hours, and twenty-four hours. After the 24-hour interval, the contents of the medicine cups were measured and recorded. 1.5 mL aliquot of the remaining sample solution from the medicine cup was returned to the medicine cup and another nine-breath cycle was collected for particle size by cascade impaction; this sample collection is identified as postcycle analysis. A total of six replicates were performed for each device at each of the five time intervals and post-cycle.

All of the individual results for each replicate and interval for respirable fraction, mass median aerodynamic diameter MMAD, and geometric standard deviation are presented for review. This study demonstrated that the average particle size was — and the fine particle fraction, defined by the percentage of particles — or less was approximately —. These results were consistent with the device specifications and are further validated by the sponsor using laser diffraction technology. b(4)

Two other findings from this study were based around relative humidity (RH) range of use for the device and trends from first cycle dosing versus multiple cycle dosing. The cascade impaction study was carried out using 49% and 80% RH. Although the results were not different, there was a trend towards a slightly lower output at the higher humidity levels. The repeat cycle study demonstrates that the results were not different but there was a trend for the output of the first three breath cycle to be slightly lower than the next three breath cycle.

No reportable results for impurities were observed for any replicates in this study. Known impurities were not detected while two unknowns, , were detected but not at reportable levels. b(4)

Failure Mode Analysis

With the initial resolution of quantity and quality of the emitted dose, other studies were undertaken to examine features of the device that make affect performance or safety. The first of these studies looked at decreasing medicine cup volumes starting at and decreasing until failure was observed.

The results of this study show that the quantity and quality of the output was normal at was diminished slightly at and was below normal at . The study also showed the quantity and quality of the output was maintained at volumes up to 6.0 ml (highest volume studied) suggesting that if a second ampoule of drug was added to the nebulizer, the nebulizer would still work without alteration of the delivered dose of drug.

The next phase of this study focused on further defining how and when failure actually occurs based upon the residual medicine cup volume. These studies showed that the particle size distribution was unaltered at but became unacceptably variable starting at . This suggested that the particle size distribution is first altered and then the quantity of drug emitted from the nebulizer begins to decrease slightly as the medicine cup volume is further reduced. At residual volume, these changes are apparent. Consequently is considered the lowest acceptable residual medicine cup volume to be used with treprostinil for inhalation. b(4)

In addition to the performance tests, the sponsor conducted a simulated lifetime test to demonstrate that the cleaning instructions provided in the User's Manual are valid. The testing showed that the Optineb-IR Nebulizer continued to function and meets its specification after being exposed to a simulated lifetime of us and its expected and specified environmental conditions. Therefore the is safe and reliable to use. In addition, testing was performed to measure the VOC levels emitted from the device per EPA Test Method TO-15 and ASTM D 5466. Testing showed that although the total VOCs were not statistically different than the ambient air present at the time of the test. b(4)

I. Performance Testing – Animal

This section is not applicable to this submission.

J. Performance Testing – Clinical

It has been recommended that the sponsor perform an abbreviated clinical study demonstrating that patients are able to inhale the prescribed dose of medication. This is due primarily to the anticipated difficulty of the use of the device by the patient, and is critical to demonstrate the device performs as specified. As this clinical study is expected to be performed in a reasonably approximated environment of use, the Human Factors Study described below should be performed first and all user-related risks should be adequately mitigated. The acceptance criteria and measurable variables in this study are to be determined and evaluated by CDER.

K. Human Factors Review

Human Factors Device Consult Reviewer: Ron Kaye (ODE/DAGID/GHDB)

In the initial review of the submission, several user-related concerns were identified by the Agency and were communicated to the sponsor in a letter dated March 5, 2009. In this letter, the Agency communicated a concern to the sponsor that the current design of the device and the materials supporting its use (e.g. user manual) could possibly induce or allow use-errors that may compromise the user's ability to deliver medication properly and could thereby pose significant risks.

Among the major concerns identified by the Agency was whether users can properly dose themselves with a total of nine breaths using the currently designed breath counter mechanism. This counter counts only up to three and the patient must restart the device two additional times to receive the required nine breaths.

Additional risks include the following:

- Possible risk associated with delivery of less than the prescribed dose given the apparently challenging requirement for the user to take nine deep breaths within the specified time limit of ninety seconds.
- Whether the inhalation or exhalation into the mouthpiece triggers a change in the count displayed by the breath-counter mechanism, whether this trigger is time-related, and whether the user needs to be aware of how this process operates to ensure proper use and delivered dosage.
- The ability of users to correctly assemble your device under conditions consistent with home-use to include proper physical connection of device components and loading of appropriate levels of medication into the cup.
- Whether the two included filters are interchangeable without impacting proper performance of your device, or if not, whether there is risk of users inadvertently reversing their location on subsequent assemblies and uses.
- The extent to which proper cleaning and maintenance is required for proper device operation, and the extent to which the user materials convey this need and the process for performing these maintenance activities in a home environment.

As of April 1, 2009, the sponsor has not performed a comprehensive Usability Analysis incorporating the evaluation and prioritization of user-related risk. Following this evaluation, it has been recommended that the sponsor perform a Human Factors Study demonstrating the safe simulated-use of the Optineb-IR device in an environment that approximates the intended home-care setting. The purpose of this study is to evaluate the severity of the risks anticipated in the initial Usability Analysis, and to identify user-related risks that may have been unanticipated by the sponsor. In the end stages of the study, the sponsor should propose adequate mitigation measures for the identified user-related risks, and may be expected to modify and revalidate the proposed device as necessary to alleviate safety-related concerns regarding its use.

Please see Section L below for further information regarding this ongoing process.

L. Deficiencies

1. In the material provided for review on January 2, 2009, you have indicated that several required biocompatibility tests for various components of the Optineb-IR Nebulizer are currently ongoing. Among these are the implantation tests for the medicine cup and sealing ring materials , mouse lymphoma and chromosomal aberration tests , and the sub-chronic toxicity tests for the mouthpiece material. Please provide complete test reports for all biocompatibility tests, including those that have been previously completed (cytotoxicity, intercutaneous reactivity, sensitization etc.). In each test report, please succinctly summarize the protocols, acceptance criteria, results and conclusions for each biocompatibility test, and specifically note deviations from the protocols recommended in ISO 10993.

b(4)

2. Please refer to your June 27, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tyvaso (treprostinil) Inhalation Solution. We also refer to our letter dated March 3, 2009 and your submission dated March 25, 2009. We have completed our review of your protocol entitled "Summative Usability Test of TYVASO Inhalation System" and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

   The March 3, 2009 letter expressed our concerns regarding the current your application specifically pertaining to the design of the device and the requirement for users to appropriately dose themselves with the inhalation solution. In the sub-section "Device-Human Factors," we provided examples of areas of user-device interaction that appeared to be potentially problematic for home users. We also requested that you perform a comprehensive analysis of use-related risk and provided you with the web-address of the CDRH guidance on managing use-related risk for medical devices.

   Your "draft" protocol describes a procedure for a "summative usability test" that involves a form of simulated use of your device to include 15 to 20 participants to represent intended users. Review of this protocol indicates that it will not be sufficient to generate adequate test results in its current form to indicate that your device can be used safely and effectively as per its intended use. Deficiencies in your protocol and recommendations for its modification are as follows:

   1. Identification and prioritization of user tasks

- The protocol does not include an analysis of use-risk, meaningful results of a use-risk analysis, or list of use/interaction scenarios resulting from such an analysis upon which to structure your test. The concerns we previously mentioned that should be considered in such an analysis are not included in any form in your protocol.
- Because potential use-risks have been neither identified nor prioritized (including concerns provided by the Agency), the protocol does not identify and focus on high priority aspects of the use of the device-drug system under consideration but rather takes an overly general non-specific approach to the use of the device.
- There are no specific examples or description of the potential "use errors" that the testing process or assessors will be prepared to record, only that "use errors" (undefined) will be observed.

   Please modify your protocol such that it includes a summary of your use-related risk identification and prioritization sufficient to focus the HF/Usability assessment on use-safety. If this process was not undertaken, it will be necessary to do so prior to including the findings in your modified test protocol. The concerns provided by the Agency should be included, or excluded with explanation. Please list and describe specific use-errors that the testing will be designed to evaluate and justify that your list is reasonably comprehensive. Specific results of use error of interest to the Agency include those that could lead to unintentional underdosing, but should include overdosing and essential maintenance and cleaning as well.

2. Essential Components of User Interaction

- The "simulated use" as described in your protocol does not include breathing through the device, rather, the user is instructed to "simulate inhaling one cycle of breaths," and to not place their mouth on the device's mouthpiece but to "tell the administrator when you would inhale or exhale". The HF/Usability test, as agreed, should be "simulated" such that no drug is delivered during this phase of testing and drug concentrations are not measured in blood. It is, however, essential that all critical aspects of the interaction between the user and the device that interact with the breath counter and other components be evaluated, and this cannot be done adequately if the user does not actually simulate use by inhaling through the device and interacting with the displayed information consistent with what would occur during actual dosing.
- The dosing process, particularly concerning inhalation through the device and the critical characteristics involved (e.g., depth of inhalation, seal of lips on mouthpiece, etc.), was not described such that the relationship between clinical outcome (dose delivery) and user performance (interaction with the device) is understood and could be evaluated directly in the testing.

  Please modify your protocol to include simulated use that decomposes successful dosing interaction into critical components that can be observed and assessed by a trained observer. The input of clinical expertise regarding specific requirements of user performance will be necessary and your assessors will need to be trained accordingly to enable them to assess essential behaviors. If you have not previously performed an analysis at this level of detail that will be the necessary first step and the results of the analysis should be discussed in your protocol as part of the task analysis and prioritization previously discussed.

3. Training

The protocol needs further clarification on the nature and extent of the training that will be given to test participants and additional rationale for how the training, the lag time between training and testing, and the testing itself will reasonably represent a realistic conditions of the intended users.

4. Screening Participants

- The protocol indicates that participants will not be included unless they are either native English speakers or "highly proficient" with respect to reading and speaking. This appears to be unrealistic and not representative of home users of medical devices. If the intended users for this device are to be "highly proficient" in reading and speaking this requirement should be defined operationally and included in the device labeling.

Please modify the recruiting screener such that it does not systematically exclude representative members of the intended user population, or include an explanation of how only "highly proficient" English readers and speakers are representative or your intended population of users.

5. Testing Procedure

- We are concerned that the stepwise process of device interactions and questioning of test participants as described is artificial and does not allow sufficient naturalistic use.
- It is therefore necessary (see #2 above) that assessors be adequately trained (or possess clinical expertise in this area) to allow them to record essential aspects of interaction including difficulties with use or errors that could impact dosing.

Please modify your protocol such that evaluation will be made on users interacting with the device in a more realistic fashion. Rather than repeated interruptions with questions, users should be allowed to proceed with uninterrupted use of the device while being assessed.

More emphasis should be placed on assessment of performance during use of the device and the questioning held until after the use session is concluded.

6. Data Reduction, Analysis, and Reporting

- The protocol is not specific with respect to how test data will be tabulated or averaged and what is intended with respect to determination of acceptable performance.
- The current description of how data will be reported is vague making it difficult to understand what will be reported and what conclusions might be drawn from it.

The portion of the protocol that describes the test report should address all types of data you plan to collect and how that data will be handled and reported. These are expected to be modified as per the additional analysis and definitions requested above. Note that subjective assessment focused on aspects of use previously identified as critical, are important. Averages of scaled ratings such as overall "ease of use" or "satisfaction" are only of lesser importance.

7. Measures of User Performance and Acceptable Performance Criteria (Pass/Fail Criteria)

- Given the lack of comprehensive assessment of subcomponents of use based and prioritization based on estimated risk (as noted above), meaningful criteria for the measurement of user performance were not included in your draft protocol.
- A variety of types of data are indicated on page 6 of your draft protocol. These are not adequately defined or described. For instance, the current protocol states that "Observed use errors" will be sought but there is no explanation of what these might be or why they are important. Similarly, the nature and relevance of "Task times (stopwatch accuracy)," participant ratings of "ease of use" and responses to interview questions are also unclear. Additionally, you state that testing will be videotaped and that participants will be photographed but you do not explain how video tapes or photographs will be analyzed or used.

Meaningful measures of performance provide a basis for reasonable assessment of the use of a device. Note that you should be testing for the presence of patterns of use error that could compromise safety and effectiveness for this device. Measures need not be taken or reported if their purpose is not relevant and defined. Please provide rationale for all data you intend to collect in your testing with respect to the overall purpose of the test.

8. Modifications to Device Design

The protocol describes a "summative" test which equates to a "validation" of use. Clearly there was no "formative" or "upstream" HF/Usability work on this device. If testing results indicate problematic performance with the device and you address this with some form of mitigation (to include design modification), the resulting modified device will not be considered to have been adequately validated the effectiveness of the modification(s) has been tested.

M. Recommendation

The combined drug/device delivery system is not approvable without a comprehensive Usability Analysis and Human Factors Study as described above. Additionally, it has been recommended that the sponsor perform an abbreviated clinical study demonstrating that patients are able to inhale the prescribed dose of medication. As this clinical study is expected to be performed in a reasonably approximated environment of use, the Human Factors Study should be performed first and all user-related risks should be adequately mitigated. Additional complete test reports for biocompatibility as described by the sponsor are required for review.

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/s/

Dan Brum
6/10/2009 11:36:44 AM
CSO
Checking into DFS on behalf of CDRH reviewers (Mr. Sugato De and Mr. Ron Kaye)