

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214324Orig1s000

OTHER REVIEW(S)



DIVISION OF CARDIOLOGY AND NEPHROLOGY

Regulatory Project Manager Review

NDA: 214324
Drug: Tyvaso DPI (treprostinil) inhalation powder
Class: prostacyclin (b) (4)
Applicant: United Therapeutics Corp.

Proposed Indications: Treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability

Treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability

Resubmission Stamp Date: December 23, 2021

Action Date: May 23, 2022

❖ **BACKGROUND**

NDA 214324 provides for a new dosage form of treprostinil, a dry powder for oral inhalation, for the treatment of 1) pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability and 2) pulmonary hypertension associated with interstitial lung disease (PHILD; WHO Group 3) to improve exercise ability.

On July 8, 2021, a Citizens Petition (CP) was submitted concerning the safety of excipient fumaryl diketopiperazine (FDKP). The review team addressed the impact of FDKP in its reviews as did the Division Director in his Memo dated October 14, 2021.

On September 16, 2021, the Office of Pharmaceutical Quality notified the Division that the Applicant's drug substance analytical testing site, (b) (4) (b) (4) was classified as Official Action Indicated (OAI) in 2020 and cGMP issues remain unresolved. The Division issued a Discipline Review Letter on September 24, 2021, notifying the Applicant of this facility issue and conveyed that "...per 21 CFR 314.125, all manufacturing and testing processes must be adequate to preserve the identity, strength, quality, purity, and stability of the material produced and the proposed facilities must comply with the current good manufacturing practice regulations. This problem could impede approval."

A Complete Response Letter was issued on October 15, 2021, due to the aforementioned facility issue. A Type A Meeting was held with the Applicant on November 17, 2021 (minutes dated December 2, 2021). The application was resubmitted on December 23, 2021 and was filed as a Class I resubmission on January 14, 2022. This resubmitted NDA indicated the withdrawal of the (b) (4) facility and its replacement with two alternate drug substance testing facilities, (b) (4) and United Therapeutics Corporation (Silver Spring, MD).

Although the original reviews did not indicate a safety concern of FDKP, the Division issued an information request (IR) to the Applicant on February 15, 2022, requesting clarification how data obtained from Study No. TIP-PH-101 (BREEZE) supported the pulmonary safety of Tyvaso DPI for the proposed indications. The Applicant provided their response on February 18, 2022, which constituted a major amendment to this application. A Review Extension – Major Amendment letter was issued on February 23, 2022, extending the user fee goal date to May 23, 2022.

This review only provides a summary of information contained in the resubmission. See previous RPM review dated October 15, 2021, for details pertaining to the review of the original submission.

❖ **REGULATORY TIMELINE and APPLICATION DETAILS**

- Original NDA Stamp Date: April 16, 2021
- Complete Response Date: October 15, 2021
- Type A Meeting (post action): November 17, 2021
- Resubmission Stamp Date: December 23, 2021
- Major Amendment: February 18, 2022
- Original PDUFA Goal Date: February 23, 2022
- Extended PDUFA Goal Date: May 23, 2022
- Action Date: May 23, 2022

User Fee

This submission is a Class 1 resubmission to a previously filed application, therefore no User Fee is required.

Facilities

This resubmitted NDA indicated withdrawal of the (b) (4) facility and its replacement with two alternate drug substance analytical testing facilities, (b) (4) and United Therapeutics Corporation (Silver Spring, MD). The Office of Pharmaceutical Manufacturing Assessment (OPMA/OPQ) recommended approval for these new listed facilities. At the time of approval, all listed facilities were in good standing. For more information, refer to Integrated Quality Review dated January 31, 2022.

Proprietary Name

A request for Proprietary Name review of Tyvaso DPI was submitted to the original NDA on April 22, 2021, and was deemed “conditionally acceptable” (Aidoo, June 17, 2021). The Applicant resubmitted their request on December 23, 2021, and DMEPA concluded that the Applicant’s proposed proprietary name was again “conditionally acceptable” (Straka/Mehta/Tu, February 17, 2022). A letter granting the name was issued on February 22, 2022.

❖ **LABELING REVIEW**

Package Insert

The Division initiated labeling negotiations with the Applicant on September 24, 2021 (first review cycle) and concluded on April 14, 2022 (second review cycle). Upon review of the package insert during the second review cycle, the Division included a Bronchospasm warning statement under Warnings and Precautions. Both the Applicant and FDA agreed to this addition.

Instructions for Use (IFU)

Labeling negotiations pertaining to the IFU were completed during the first review cycle (refer to submission dated September 29, 2021).

Carton and Container Labeling

During the first review cycle, the Applicant submitted revisions to carton and container labels on August 13, 2021, and additional revisions to carton labels on October 1, 2021. There were no further comments from FDA after the Applicant's October 1, 2021 response. Upon further review during the second review cycle, DMEPA provided additional formatting and layout comments to the October 1, 2021, submission, which were issued to the Applicant via email on February 11, 2022. The Applicant incorporated the requested revisions on February 17, 2022; however, due to a global supply chain issue, they requested to launch Tyvaso DPI with carton labeling printed from the previous review cycle on October 1, 2021. FDA agreed to this request and required the Applicant submit a formal notification to the NDA when carton labeling has been received and implemented. For additional information, please refer to DMEPA Memo (Mehta, 5/23/22).

For purposes of the action letter, the agreed upon carton and container labeling from submissions dated April 16, 2021 (blister labels), August 13, 2021 (titration kit and maintenance tray labels), and February 17, 2022 (institutional kit, maintenance, and titration kit carton labels) were included.

❖ REVIEWS

The following is a list of discipline reviews obtained during this review. For more detail on reviews completed from the previous review cycle, refer to RPM review in DARRTS dated 10/15/21.

Clinical/Decisional Memo (May 23, 2022 – Southworth, Stockbridge)

Recommended Action: Approval

During the original review cycle, the clinical reviewer recommended approval based on the submitted data (Psocka, September 23, 2021). No new clinical data were included within the resubmission; however, DCN became aware of a CP submitted during the original review cycle (regulations.gov; FDA-2021-P-0714) which raised concerns about FDKP, an excipient included in Tyvaso DPI. An assessment of the Tyvaso DPI drug product in the original clinical review did not indicate a safety concern.

To understand more fully the pulmonary safety of Tyvaso DPI and implications for labeling, FDA's Adverse Event Reporting system (FAERS) was searched for cases of acute bronchospasm associated with marketed Tyvaso inhalation solution (IS-treprostinil solution), the drug substance in Tyvaso DPI. Several cases of acute bronchospasm shortly after Tyvaso IS use were identified (see postmarketing review dated 5/3/2022). Another prostaglandin (Ventavis, NDA 21779) is associated with bronchospasm. Despite the absence of clinical cases with Tyvaso DPI at this time, bronchospasm has been identified as a potential risk for the class of inhaled prostaglandins; therefore, language to address bronchospasm was included into the Warnings and Precautions section of labeling. Both the Applicant and FDA agreed to include this new warning statement.

OPQ - Integrated Quality Review (January 31, 2022 - Multiple reviewers)

Recommended Action: Approval

OPQ provided an integrated review and concluded the complete response issues are now adequately resolved from a quality perspective; therefore, recommending approval of this NDA. Their review detailed the withdrawal of (b) (4) drug substance testing facility and replacement with two new testing facilities, (b) (4) and United Therapeutics Corporation (Silver Spring, MD). In addition, their review states "These two new facilities will now be responsible to conduct the drug substance testing for (b) (4) content, endotoxin, and microbial limits. All these three compendial (USP) tests and their methods were appropriately transferred. The tests were conducted on the new drug substance batches at these new testing sites. The testing data demonstrated acceptable results."

The review also stated that an expiration period of **18 months** for the product, when refrigerated at controlled temperature of **2°C to 8°C (36°F to 46°F)** in the commercial packaging is granted. In addition, the drug product in unopened blister cards/strips is permitted to be stored up to 5 weeks at room temperature.

UTC claimed categorical exclusion and OPQ found the exclusion acceptable.

For additional information, please refer to the OPQ integrated review for the previous NDA review cycle, dated September 30, 2021.

❖ **CONCLUSION**

After taking into consideration all primary and consult reviews during the original and resubmission review, the Division issued an approval letter, signed by Norman Stockbridge, Division Director for NDA 214324 on May 23, 2022.

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/s/

BRIAN T COONEY
05/23/2022 12:34:30 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: May 23, 2022
Requesting Office or Division: Division of Cardiology and Nephrology (DCN)
Application Type and Number: NDA 214324
Product Name and Strength: Tyvaso DPI (treprostinil) inhalation powder, 16 mcg, 32 mcg, 48 mcg, and 64 mcg
Applicant/Sponsor Name: United Therapeutics Corp.
OSE RCM #: 2021-795-4
DMEPA 2 Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant communicated on February 11, 2022 that their revised carton labeling received on February 17, 2022 for Tyvaso DPI will not be ready in time for launch if the NDA is approved. As such, they requested to launch their product with the original labeling from October 1, 2021 until they obtain labels printed in (b) (4) which may be delayed until the (b) (4) due to supply chain issues.

2 CONCLUSION

The Applicant will need to launch their product with the already printed carton labeling submitted on October 1, 2021 due to supply issues. The revised carton labeling received on February 17, 2022 will begin to be utilized once they are printed in (b) (4). The difference between the two carton labeling was to bring prominence to the strength and net contents statement. As there was no change to any other content on the labeling we find this proposal acceptable.

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/s/

HINA S MEHTA
05/23/2022 10:06:44 AM

Memorandum

From: Mary Ross Southworth, PharmD
Deputy Director for Safety
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology, and Nephrology/CDER/FDA

Date: May 3, 2022

Subject: Acute Bronchospasm and inhaled prostaglandins (Tyvaso Inhalation Solution 22-387)

Tyvaso inhalation solution (IS) is approved to improve exercise ability for pulmonary arterial hypertension (WHO group 1) and PH-ILD; WHO Group 3) patients. DCN reviewed cases of acute bronchospasm associated with Tyvaso inhalation solution (IS), prompted by a citizen petition (Dkt. No. FDA-2021-P-0714 at [regulations.gov](https://www.regulations.gov)) submitted to the FDA which raised issues related to the pulmonary safety of an inhaled product for pulmonary hypertension. The following postmarketing cases were retrieved from FAERS that describe bronchospasm in patients receiving Tyvaso IS and were reviewed:

(b) (6)
(b) (6)

9 yo female

Difficulty getting deep breaths after treatments for 10 to 15 minutes. Evidence of FEV1 drop post dose.

(b) (6)
(b) (6)

54 yo female

Dyspnea and bronchospasm after starting inhaled Tyvaso. Resolved upon discontinuation

(b) (6)
(b) (6)

59 yo male

Increased shortness of breath and bronchial spasms. Hospitalized.

(b) (6)
(b) (6)

71 yo male

Dose decreased and then discontinued due to bronchospasm and cough.

(b) (6)
(b) (6)

Elderly female

Bronchospasm, unrelieved by rescue inhaler. Decreased dose.

(b) (6)

(b) (6)

43 yo female

Bronchospasm upon initiation. Hospitalized. Resolved upon discontinuation.

(b) (6)

(b) (6)

50 yo female

Experienced shortness of breath, wheezing, bronchospasm when starting Tyvaso. Drug discontinued.

The temporal association between inhalation of Tyvaso IS and the bronchospasm event, supports causality. We also note that another inhaled prostaglandin for use in PAH WHO Group 1 (Ventavis, NDA 21779) includes the following warning in its label:

5.3 Bronchospasm

VENTAVIS inhalation can induce bronchospasm. Bronchospasm may be more severe or frequent in patients with a history of hyperreactive airways. VENTAVIS has not been evaluated in patients with chronic obstructive pulmonary disease (COPD), severe asthma, or with acute pulmonary infections.

The presence of similar cases for both of these inhaled products and the known irritant properties of prostaglandins support the conclusion that bronchospasm is a potential risk for the class of inhaled prostaglandins.

To reflect this risk, the following will be added to the label for Tyvaso Inhalation Solution.

5.4 Bronchospasm

Like other inhaled prostaglandins, Tyvaso inhalation solution may cause acute bronchospasm. Patients with asthma or chronic obstructive pulmonary disease (COPD), or other bronchial hyperreactivity are at increased risk for bronchospasm. Ensure that such patients are treated optimally for reactive airway disease prior to and during treatment with Tyvaso inhalation solution.

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/s/

MARY R SOUTHWORTH
05/03/2022 07:35:39 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: February 18, 2022
Requesting Office or Division: Division of Cardiology and Nephrology (DCN)
Application Type and Number: NDA 214324
Product Name and Strength: Tyvaso DPI (treprostinil) inhalation powder, 16 mcg, 32 mcg, 48 mcg, and 64 mcg
Applicant/Sponsor Name: United Therapeutics Corp.
OSE RCM #: 2021-795-3
DMEPA 2 Safety Evaluator: Maximilian Straka, PharmD, FISMP
DMEPA 2 Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on February 17, 2022 for Tyvaso DPI. We reviewed the revised carton labeling for Tyvaso DPI (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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^a Straka, M. Review of Revised Label and Labeling Memo for Tyvaso DPI (NDA 214324). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 FEB 10. RCM No.: 2021-795-2.

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/s/

MAXIMILIAN STRAKA
02/18/2022 10:05:13 AM

HINA S MEHTA
02/18/2022 11:03:54 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: February 10, 2022
Requesting Office or Division: Division of Cardiology and Nephrology (DCN)
Application Type and Number: NDA 214324
Product Name and Strength: Tyvaso DPI (treprostinil) inhalation powder, 16 mcg, 32 mcg, 48 mcg, and 64 mcg
Applicant/Sponsor Name: United Therapeutics Corp. (UTC)
OSE RCM #: 2021-795-2
DMEPA 2 Safety Evaluator: Maximilian Straka, PharmD, FISMP
DMEPA 2 Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

UTC submitted a response to the Complete Response (CR) on December 23, 2021 for NDA 214324 Tyvaso DPI (treprostinil) inhalation powder. NDA 214324 received a CR on October 15, 2021 due to facility inspection issues. As part of the response to complete response, UTC resubmitted the Prescribing Information (PI), Instructions for Use (IFU) and referenced the carton labeling previously submitted on October 1, 2021.

2 CONCLUSION

The carton labeling is unacceptable from a medication error perspective. We note the strength statement may cause confusion as currently presented it is only displayed with the number in the box and the unit of measure per cartridge is stated outside of the strength. The established name is difficult to read. In addition, the prominence of the contents statement and type of “kit” should be increased. We provide our recommendations below.

3 RECOMMENDATIONS FOR UNITED THERAPEUTICS, CORP.

We recommend the following be implemented prior to approval of this NDA:

A. Carton Labeling

- a. As currently presented strength lacks prominence and the unit of measure per cartridge is stated outside of the colored box. We recommend increasing the

prominence of the strength and including the “mcg per cartridge” be stated in the colored box as the numerical strength.

- b. As currently presented the type of kit and contents of kit lacks prominence. We recommend increasing the prominence (i.e. increasing the font) of the kit type and contents.
- c. As currently presented the established name is difficult to read. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

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/s/

MAXIMILIAN STRAKA
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HINA S MEHTA
02/10/2022 03:07:47 PM



DIVISION OF CARDIOLOGY AND NEPHROLOGY

Regulatory Project Manager Review

NDA: 214324
Drug: Tyvaso DPI (treprostinil) inhalation powder
Class: Prostacyclin analogue
Applicant: United Therapeutics Corp. (UTC)

Proposed Indications: Treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability
Treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability

Received Date: April 16, 2021
Complete Response date: October 15, 2021
PDUFA date: October 16, 2021

❖ REVIEW TEAM

Center for Drug Evaluation and Research

Office of Cardiology, Hematology, Endocrinology and Nephrology, Division of Cardiology and Nephrology (DCN)

- Norman Stockbridge, MD, PhD – Division Director
- Mary Ross Southworth, PharmD – Deputy Director for Safety
- Michael Monteleone, MS, RAC – Associate Director for Labeling
- Fred Senatore, MD, PhD – Clinical Team Leader
- Mitchell Psotka, MD, PhD – Clinical Reviewer

Office of Pharmaceutical Quality (OPQ)

Office of New Drug Products

- Mohan Sapru, PhD – Cross-Disciplinary Team Leader (CDTL)
- Akm Khairuzzaman, PhD – Application Technical Lead/Drug Product Reviewer
- Daniel Jansen, PhD – Drug Substance Reviewer

Office of Pharmaceutical Manufacturing Assessment

- Alex Gontcharov, PhD – Process and Facility Reviewer
- Parnali Chatterjee, PhD – Biopharmaceutics
- Amanda Buskirk, PhD – Microbiology Reviewer

Division of Pharmacology/Toxicology for Cardiology, Hematology, Endocrinology, and Nephrology

- Xuan Chi, MD, PhD – Non-clinical Team Leader
- Baichun Yang, PhD – Non-clinical Reviewer

Office of Clinical Pharmacology, Division of Cardiometabolic & Endocrine Pharmacology

- Manoj Khurana, PhD – Clinical Pharmacology Team Leader
- Xiaomeng Xu, PhD – Clinical Pharmacology Reviewer

Office of Regulatory Operations, Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, & Nephrology

- Brian Cooney, MS, PSM – Regulatory Health Project Manager
- Bridget Kane, MS – Sr. Regulatory Health Project Manager
- Alexis Childers, RAC – Sr. Regulatory Health Project Manager

Office of Surveillance and Epidemiology (OSE)

Division of Medical Error Prevention and Analysis (DMEPA)

- Lolita White, PharmD – Associate Director for Human Factors
- Chi-Ming (Alice) Tu, PharmD – Associate Director for Nomenclature and Labeling
- Colleen Little, PharmD – Team Lead
- Ebony Whaley, PharmD – Safety Evaluator
- Murewa Oguntimein, PhD – Human Factors Specialist

Division of Risk Management

- Cynthia LaCivita, PharmD – Director
- Laura Zendel, PharmD – Team Leader
- Brian Caruth, PharmD – Reviewer

Office of Medical Policy

Office of Prescription Drug Promotion (OPDP)

- Jim Dvorsky, PharmD – Team Leader
- David Foss, PharmD – Regulatory Review Officer

Office of Medical Policy Initiatives, Division of Medical Policy Programs, Patient Labeling Team (PLT)

- Barbara Fuller, RN, MSN, CWOCN – Team Lead
- Ruth Mayrosh, PharmD – Reviewer

Center for Devices and Radiological Health (CDRH)

Office of Product Evaluation and Quality (OPEQ), Office of Health Technology 1, Division of Health Technology 1 C (Anesthesia, Respiratory, & ENT Devices)

- Dongbo Wang, PhD – Team Lead
- John S. Bender, PhD – Chemist

❖ **BACKGROUND**

Treprostinil, a prostacyclin vasodilator developed by United Therapeutics Corporation (UTC), was originally approved in May 2002 (Remodulin; NDA 021272) as an injection for the treatment of pulmonary arterial hypertension (PAH) in patients with NYHA Class II-IV symptoms to diminish symptoms associated with exercise. Subsequently, the following dosage forms were approved: a solution for inhalation [NDA 022387 (Tyvaso), July 2009], extended-release tablets for oral administration [NDA 203496 (Orenitram), December 2013].

Tyvaso (treprostinil) inhalation solution is also currently approved for the treatment of PAH (WHO Group 1) to improve exercise ability and for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability.

In June 2010, Tyvaso was granted orphan drug designation (#04-1891) for the treatment of PAH.

Under IND 134582, UTC developed a new dosage form, an inhalation powder - treprostinil dry powder for inhalation (DPI). Treprostinil DPI is a drug-device combination product comprised of single-use cartridges of 16, 32, 48, or 64 mcg of treprostinil dry powder to be used with a dry powder inhaler. The drug product and device are manufactured by MannKind Corporation (DMF (b) (4))

UTC conducted the following studies to evaluate the safety and tolerability of treprostinil DPI and to demonstrate similar exposure when compared to Tyvaso (treprostinil) inhalation solution:

- MKC-475-001: a phase 1, open-label, single-ascending dose study in healthy normal volunteers conducted to assess the safety and tolerability of treprostinil inhalation powder
- TIP-PH-101: a multicenter phase 1b, safety and tolerability study in which PAH subjects on a stable regimen of Tyvaso switched to a corresponding dose of treprostinil inhalation powder
- TIP-PH-102: a phase 1, single-center, randomized, crossover study comparing systemic exposures of treprostinil inhalation powder and Tyvaso in healthy normal volunteers.

On April 16, 2021, UTC submitted NDA 214324 for Tyvaso DPI (treprostinil) inhalation powder (for oral inhalation) for the treatment of 1) pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability and 2) pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. To support this NDA, UTC provided cross-reference to Tyvaso, Remodulin, and Orenitram NDAs in addition to conducting the above-referenced studies.

The Applicant requested Priority Review and submitted a Rare Pediatric Disease Priority Review Voucher (PRV BLA 761171). This Application was filed on June 15, 2021 and deemed a priority review.

On July 8, 2021, a Citizens Petition was submitted concerning the safety of excipient fumaryl diketopiperazine (FDKP). The review team addressed the impact of FDKP in its reviews as did the Division Director in his Memo dated October 14, 2021.

On September 16, 2021, OPQ notified the Division that the Applicant's drug substance analytical testing site, (b) (4) (b) (4) was classified as Official Action Indicated (OAI) in 2020 and cGMP issues remain unresolved. The Division issued a Discipline Review Letter on September 24, 2021 notifying the Applicant of this facility issue and conveyed that "...per 21 CFR 314.125, all manufacturing and testing processes must be adequate to preserve the identity, strength, quality, purity, and stability of the material produced and the proposed facilities must comply with the current good manufacturing practice regulations. This problem could impede approval."

This issue was not able to be resolved during the review cycle. See Facilities and Discipline Review sections for further details and recommendations.

❖ **REGULATORY TIMELINE and APPLICATION DETAILS**

- | | |
|--------------------------|-------------------|
| • Pre-NDA Meeting (WRO): | November 19, 2020 |
| • NDA Stamp Date: | April 16, 2021 |
| • Filing Meeting: | May 17, 2021 |
| • Filing Date: | June 15, 2021 |
| • Filing Letter: | June 15, 2021 |
| • Mid-cycle Meeting: | July 15, 2021 |

- PeRC Meeting September 21, 2021
- PDUFA Date: October 16, 2021

User Fee

UTC submitted payment on April 15, 2021 (User Fee ID #3017970).

Facilities

The drug substance analytical testing facility, (b) (4) (FEI (b) (4) is currently classified as OAI; quality system and device deficiencies remain unresolved. All other sites were acceptable.

Site Inspections

The Clinical Pharmacology team requested Biopharmaceutical Inspections for the clinical and analytical sites for Study #TIP-PH-102 (Consult submitted May 26, 2021). The Office of Study Integrity and Surveillance (OSIS) stated that inspections were not warranted because the sites were recently inspected (2018) and found to be acceptable (Adeyemo, June 24, 2021).

Proprietary Name

The Applicant submitted a request for Proprietary Name review of Tyvaso DPI on April 22, 2021. DMEPA concluded that the Applicant's proposed proprietary name was conditionally acceptable (Aidoo, June 17, 2021).

Pediatric Review Committee (PeRC)

This application triggered PREA. Since the Applicant received Orphan Drug Designation for the PAH indication, this indication was exempt from PREA requirements. For the PH-ILD indication, the Sponsor submitted a request for a full waiver for pediatric studies because the necessary studies are impossible or highly impracticable, as the number of pediatric patients with PH-ILD is extremely rare (Agreed iPSP, July 7, 2020; IND 134582). The Division and PeRC agreed with the Applicant's request for waiver on September 21, 2021.

Advisory Committee

There was no Advisory Committee meeting for this NDA because this drug does not raise significant safety or efficacy issues.

Review Status

The Applicant submitted a Rare Pediatric Disease Priority Review Voucher (PRV BLA 761171). The Application was deemed a Priority Review.

❖ **LABELING REVIEW**

The Division initiated labeling negotiations with the Applicant on September 24, 2021; the last version of the PI was submitted by the Applicant via email October 8, 2021 – the Division is in general agreement with this draft at the time of this action. The last version of the IFU was submitted on September 29, 2021; the Division had no further comments. Carton and containers comments were conveyed to UTC during the review cycle. There were no further comments after the Applicant's October 1, 2021 response (SDN 12).

❖ **DISCIPLINE REVIEWS**

Below are the conclusions reached by the primary review team. Please refer to DARRTS for complete reviews.

Divisional Memorandum (14Oct21 – Stockbridge)

Recommended Action: Complete Response

Dr. Stockbridge's review addressed the impact of FDKP as an excipient. He stated that both he and the review team have "a low level of suspicion that FDKP will cause bronchospasm in patients with PAH, and this risk is not specifically named in proposed labeling of Tyvaso DPI". Dr. Stockbridge concluded that the Division and OND concur with OPQ's recommendation for a Complete Response due to (b) (4) OAI status.

CDTL Memorandum (14Oct21 – Sapru)

Recommended Action: Complete Response

Dr. Sapru's memo summarized each discipline's review. He stated that after several inter-office meetings regarding the OAI status of (b) (4) he agreed with OPQ's assessment to recommend a Complete Response.

OPQ - Integrated Quality Review (30Sept21 – Multiple reviewers)

Recommended Action: Complete Response

OPQ provided an integrated review and concluded that all CMC information on this new drug product formulation is referenced in DMF # (b) (4) and found to be adequate to support approval. In addition, the review states that "the proposed control strategies for the drug product manufacturing are adequate to ensure consistent drug product quality regarding identity, assay, purity, dissolution, content uniformity, (b) (4), microbial content, and stability. The proposed 18-month shelf life is supported by sufficient stability data and found to be acceptable."

Although the information located in the DMF was found to be acceptable, OPQ concluded this NDA cannot be approved until the OAI status of the (b) (4) facility is changed to cGMP compliant.

Nonclinical Review (22Jun 21 - Yang/Chi)

Recommended Action: Approval

Dr. Yang stated that the safety and efficacy of treprostinil are supported by a comprehensive set of nonclinical pharmacology, pharmacokinetic, and toxicology studies conducted to support Tyvaso (NDA 022387), Remodulin (NDA 021272), and Orenitram (NDA 203496) and the assessment of impurities provided for Tyvaso DPI. Therefore, it is considered that Tyvaso DPI has an acceptable safety profile and no findings that preclude long-term inhalation administration in humans. Her review also states "The safety of the excipient (FDKP) is supported by a comprehensive battery of safety pharmacology and toxicology studies conducted for Afrezza (BLA 022472).

Clinical-Pharmacology Review (23Sept21 – Xu/Khurana)

Recommended Action: Approval

Dr. Xu reviewed 3 studies submitted in support of this NDA. Study TIP-PH-101, assessed the efficacy, safety, and tolerability of treprostinil inhalation powder (TIP). Study TIP-PH-102 assessed the relative bioavailability (BA) and bioequivalence (BE) of TIP and Tyvaso. And Study MKC-475-001 was only reviewed for supportive information as it did not contribute to the systemic exposure comparison of TIP and Tyvaso. Data from the relative BA/BE study (TIP-PH-102) indicated a higher Cmax of treprostinil from TIP than Tyvaso, and a comparable overall AUC (except the modest deviation at the low-dose level). Dr. Xu concluded that these findings do not appear to be clinically relevant given that clinical use of TIP involves titration to therapeutic goal. Dr. Xu also stated that the limited safety data from single and multiple dose studies did not show notable respiratory adverse events.

Clinical Review (23Sept21 – Psotka/Senatore)

Recommended Action: Approval

Dr. Psotka stated that evidence of safety and effectiveness comes from the liquid formulation (Tyvaso), and no additional studies evaluating effectiveness were submitted with this application. Safety and tolerability of the inhaled powder formulation was evaluated in Study # TIP-PH-101 (BREEZE). He stated that “patients on a stable regimen of inhaled liquid treprostinil were transitioned to an approximate corresponding dose of open-label inhaled treprostinil powder (TYVASO-DPI) and followed initially for 3 weeks. The switch from inhaled treprostinil liquid to the inhaled powder formulation was not associated with a decrement in exercise capacity as measured by the 6-minute walk test distance.”

Dr. Psotka’s review also discussed the excipient FDKP which is also described in the approved Afrezza label. The Afrezza label contains a box warning for chronic lung disease and bronchospasm but does not specify if FDKP is responsible for an increased risk of bronchospasm. Dr. Psotka stated the exposure of FDKP by treprostinil inhaled powder appears acceptable as the BREEZE trial included patients with several lung diseases and there were no adverse events reported in the trial.

OSE/DRM (4Oct21 – Caruth)

Dr. Caruth evaluated whether a risk evaluation and mitigation strategy (REMS) is necessary to ensure the benefits outweigh the risks for Tyvaso DPI. The efficacy and safety rely on previous findings from the referenced approved formulations and excipients, including FDKP. In addition, his review states efficacy was evaluated in Study TIP-PH-101 in which the most commonly reported adverse events were similar to the approved formulations.

Based on these findings, and the fact that this product will be prescribed in an outpatient setting by pulmonologists and cardiologists familiar with PAH and the risks of this therapy, Dr. Caruth did not recommend a REMS for the management of the risks associated with Tyvaso DPI. In addition, the referenced treprostinil drugs do not have a REMS. He stated the risks can be communicated via labeling.

OSE/DMEPA (23Sept21 – Oguntimein, Whaley)

Dr.’s Oguntimein and Whaley conducted a review of the human factors validation report and labeling (PI, IFU, and carton and containers). They found the validation study methodology to be acceptable based on consideration of controls that were outlined in the NDA. In the validation study, only trained users by two specialty pharmacy (b) (4) and (b) (4) nurses were certified to receive a prescription for Tyvaso DPI after demonstrating proper use. This plan is representative of real-world use. The reviewers found this acceptable. See full review for comments on labeling.

❖ **CONSULT REVIEWS**

The following is a list of consult reviews obtained during this review. Refer to DARRTS for complete reviews.

CDRH Review (01Oct21) – Bender

Recommended Action: Completed No Deficiencies (CND)

In CDRH’s opinion, and from the biocompatibility perspective there are no safety issues. The Tyvaso DPI inhaler that was tested is identical to the intended commercial inhaler, which is completely described in DMF (b) (4). Dr. Bender’s review stated, “with the exception of the (b) (4) (b) (4), as described in DMF (b) (4) Section 3.2.R “TreT Inhalation System and (b) (4) Comparison,” the Tyvaso DPI Inhaler and the (b) (4)

Therefore, no additional biocompatibility testing was required.”

Labeling Reviews

- OPDP: Foss/Dvorsky –September 8, 2021
- Patient Labeling: Mayrosh –September 16, 2021

❖ **CONCLUSION**

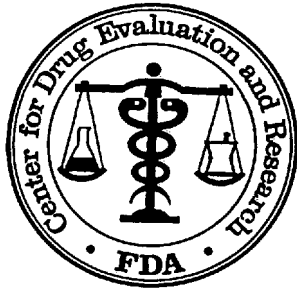
After taking into consideration all primary and consult reviews, the Division issued a Complete Response letter for NDA 214324 on October 15, 2021 signed by Norman Stockbridge, MD, PhD – Division Director.

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DIVISION OF CARDIOLOGY AND NEPHROLOGY
Divisional Memorandum

NDA: 214324 (inhaled treprostinil powder)
Sponsor: United Therapeutics
Reviewer: N. Stockbridge, M.D., Ph.D.

The product is the combination of a new powder formulation of treprostinil and a dry powder inhaler device. I concur with Dr. Sapru's CDTL memo.

The new formulation is roughly (b) (4) % fumaryl diketopiperazine (FDKP), a non-compensial excipient that acts as a carrier. To our knowledge, FDKP has only been used in one approved product, AFREZZA (inhaled insulin). Per the non-clinical review, FDKP's "non-clinical safety was supported by a comprehensive battery of safety pharmacology and toxicology studies."

AFREZZA has a boxed warning and REMS regarding the potential for bronchospasm in patients with COPD and asthma. The signal for bronchospasm arose from a small PK study of asthmatic patients and was quite remarkable with 29% of patients reporting bronchospasm or wheezing. Decreases in FEV1 associated with Afrezza use were also observed in studies of patients with asthma and COPD prompting a required postmarketing study to evaluate the long-term effects (5 years) on FEV1.

It is unclear if AFREZZA's cases of bronchospasm or FEV1 decline were related to FDKP or to insulin. Decreases in FEV1 were observed in both arms of a study comparing AFREZZA to FDKP alone, but a smaller decrease was seen in the FDKP alone group—decline over 24 weeks of about 1.5% on FDKP alone and about 3 times that on AFREZZA (no placebo).

Treprostinil is approved in an inhaled liquid formulation (with no FDKP), so little beyond demonstrating bioavailability was necessary for Tyvaso DPI. Safety of Tyvaso DPI is supported by a 51-subject, 3-week study with an open-label extension. The safety profile in this study is indistinguishable from that for the inhaled liquid—a mix of vasodilatory and airway irritation effects. No bronchospasm was observed in this study.

For what it is worth, at their highest practical doses (treprostinil's dose is limited by tolerability), the amount of FDKP daily is somewhat less with Tyvaso DPI than with AFREZZA.

The review team and I have a low level of suspicion that FDKP will cause bronchospasm in patients with PAH, and this risk is not specifically named in proposed labeling of Tyvaso DPI.

An analytic site is in OAI status, and OPQ recommends and OND concurs on a Complete Response.

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Chemical Characterization/Biocompatibility Consult

Consult Number: CON2123307

Document Number: ICC2100386

Applicant:

Trade Name:

Consult Type: Chemistry

Requestor: Dongbo Wang [DONGBO.WANG]
dongbo.wang@fda.hhs.gov

Requestor Home: CDRH\OHT1\DHT1C\THT1C3

Requested Consultant: John Bender [JOHN.BENDER]
john.bender@fda.hhs.gov

Gatekeeper / Consultant: John Bender [JOHN.BENDER]
john.bender@fda.hhs.gov

Consultant Home: CDRH\OHT1\DHT1C\THT1C3

Date Requested: October 1, 2021

Due Date: October 1, 2021

Instructions: Do review.

Recommendation: CND

Contents

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1. Scope

This memo is provided regarding the gas pathway and leachable/extractable testing for the device component of NDA 214324 (Tyvaso DPI™ (Treprostinil) Inhalation Powder, which has been submitted for Agency approval by United Therapeutics Corp. The application is cross referenced with (b) (4) DMF (b) (4). The analyses are provided in support of the biocompatibility of the device. The analytical protocols and test reports are reviewed and analyzed in terms of the Agency's view of biocompatibility evaluation.

2. Materials Reviewed

- A. Pertinent emails/letters throughout review cycle
- B. Applicant response to RFI, dated 2021-05-24
- C. DEVICE Test Report for Emissions of Particulate Matter from Tyvaso DPI
- D. DEVICE Test Report for Emissions of VOCs and Aldehydes from Tyvaso DPI
- E. DEVICE ISO 18562-1 Biocompatibility Evaluation of Tyvaso DPI
- F. ADTR-360-005 Controlled Extraction Study of (b) (4) Device Components and Secondary Packaging Materials, November 16, 2010 OTH-020 Biological Evaluation Report
- G. PharmTox.2011.0005 Toxicological Evaluation of Extractables from a Controlled Extraction Study on the (b) (4) (b) (4) Dry Powder Inhaler, January 10, 2011

3. History

This review is provided in response to the applicant's response to RFI, dated May 24th, 2021.

4. Indications for Use

Tyvaso DPI is a prostacyclin mimetic indicated for the treatment of PAH (WHO Group 1) and PH-ILD (WHO Group 3) to improve exercise ability.

5. Drug/Device Description

The following is taken from the application description of the Drug Product (3.2.P.1 of DMF (b) (4))

Treprostinil Inhalation Powder is a dry powder treprostinil formulation for pulmonary delivery. The inhalation powder comprises treprostinil and the excipient fumaryl diketopiperazine (FDKP). Trace amounts of (b) (4) may be present.

Treprostinil Inhalation Powder is targeted to contain 10 µg of treprostinil per mg of powder. Treprostinil Inhalation Powder is filled into unit-dose cartridges ((b) (4) Cartridge Lid and Cup, see Section 3.2.P.7 Container Closure System) to contain 16 µg, 32 µg, 48 µg or 64 µg of treprostinil per cartridge. The 16 µg, 32 µg, 48 µg and 64 µg cartridges have nominal fill weights of 1.6 mg, 3.2 mg, 4.8 mg and 6.4 mg of Treprostinil Inhalation Powder, respectively.

The following is taken from the application description of the Container Closure System (3.2.P.7 of DMF (b) (4))

The inhaler used to deliver Treprostinil Inhalation Powder (the “TreT Inhaler”) contains (b) (4)

(covered under DMF

(b) (4) It is a mechanical device consisting of

(b) (4)

(b) (4)

). Performance of the TreT inhalation system has been assessed in a series of device characterizations provided in Section 3.2.P.2.4 to confirm the inhaler delivers the Treprostinil Inhalation Powder consistently and effectively. (b) (4)

(b) (4)

The intended commercial inhaler includes TYVASO DPI (b) (4) (b) (4) (b) (4)

(b) (4)

(b) (4)

(b) (4)

The inhaler currently utilized in clinical trials does not include (b) (4) (b) (4) Figure 5 depicts the assembled inhaler (b) (4)

The components of the assembled inhaler are also depicted in an exploded schematic within Figure 5. A comparison of the TreT Inhaler and the Afrezza Inhaler is provided in 3.2.R TreT Inhalation System and Afrezza Inhalation System Comparison.

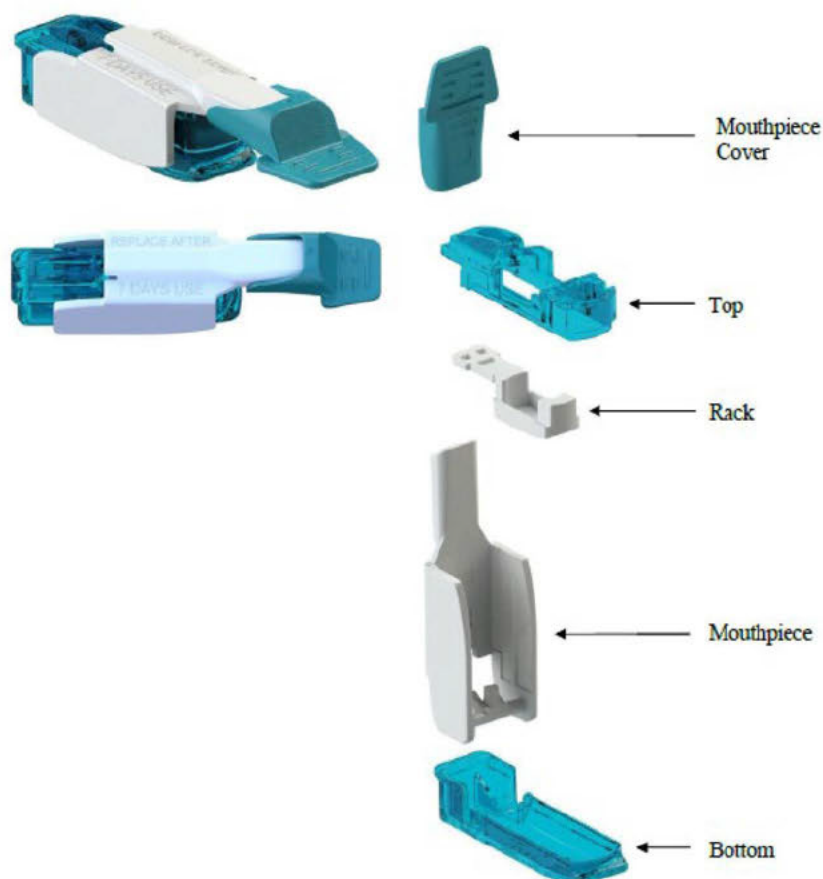


Figure 5. TreT Inhaler (including exploded schematic)

The inhaler drawings and specifications are listed in [Table 6](#) and the documents are provided in Section 3.2.R Regional Information. Specifications and rationale are common with the Afrezza Inhaler. The analytical method for identification by FTIR (TM5555) listed in the specifications for the Mouthpiece (b) (4) and is included in DMF (b) (4)

(b) (4). The materials of construction, (b) (4) suppliers and colorant suppliers are provided in [Table 7](#). Letters of Authorization to reference the DMFs noted in [Table 7](#) are provided in Section 1.4.2.

Table 6. Inhaler Drawings and Specifications

Component	Drawing (Clinical)	Specification (Clinical)	Drawing (Commercial)	Specification (Commercial)
(b) (4)				

Table 7. Materials of Construction and (b) (4) Suppliers for the TreT Inhaler Components

(b) (4)	
---------	--

(b) (4)

The Mouthpiece is the only component of the inhaler that is in contact with the drug product and the patient mucosa. (b) (4) The overall biological safety assessment of the inhaler, and the chemical characterization (extractables/leachables) of the Mouthpiece component in particular, was performed as part of development and is included in 3.2.P.2.4 Pharmaceutical Development – Container Closure System. The biocompatibility reports for the Mouthpiece are included in DMF (b) (4) The (b) (4) used to manufacture the Mouthpiece complies with 21 CFR 177.1660, USP <87> and USP (b) (4) and Class (b) (4) testing. The Mouthpiece component was tested and met ISO 10993 biocompatibility, USP <87>, and USP (b) (4) standards. Additionally, the ISO 18562 series of standards, for the testing and evaluation of gas pathways of medical devices, has been performed to assess emission of inhalable particulates and VOC (Volatile Organic Compounds). The testing for the particle emissions followed the guidelines of ISO 18562-2 and the testing for VOCs was conducted as per ISO 18562-3. The testing demonstrated the inhaler to be safe for the intended use. The reports are listed in Table 8 and are provided in Section 3.2.R Regional Information.

Reviewer comment: The applicant states that (b) (4)

(b) (4) conducted E&L testing in 2010/2011. United Therapeutics conducted ISO 18562 testing in 2021.

6. Chemical Characterization//Gas Pathway/Biocompatibility

Consensus Standards: ISO 18562-1, ISO 18562-2, ISO 18562-3, ISO 10993-18

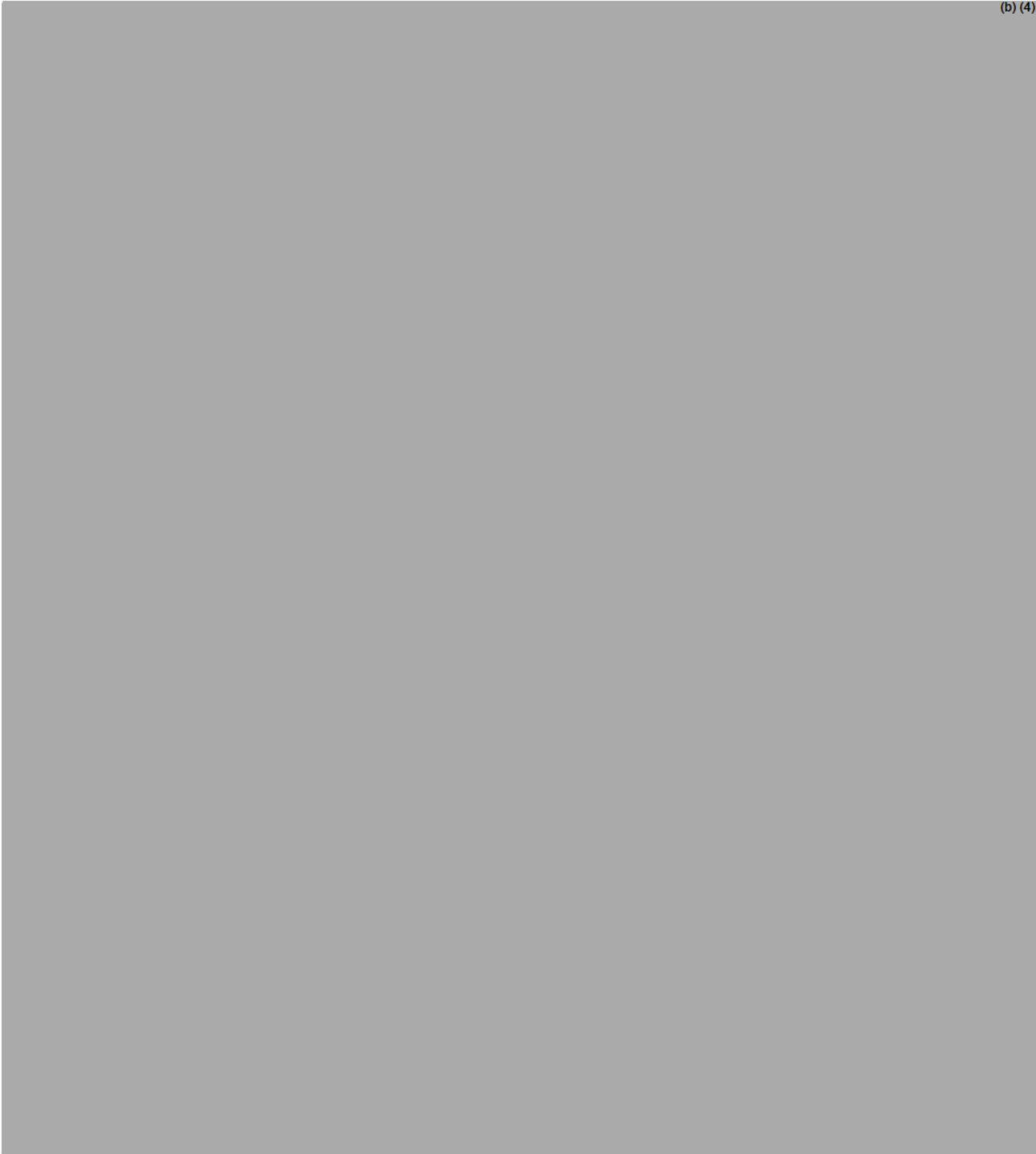
Test reports to be evaluated:

1001138480-3721587P	Emissions of Particulate Matter
1001138480-3638017R1	Emissions of VOCs
ADTR-360-005	E&L

Particulate Matter (ISO 18562-2)

(b) (4)

(b) (4)



Reviewer comment: The successfully tested against ISO 18562-2.

VOCs (ISO 18562-3)

(b) (4)



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Reviewer comment: The sponsor has successfully tested against ISO 18562-2.

Chemical Characterization/Condensate (ISO 10993-18)



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Reviewer comment: The determination of maximization of extractables is not in line with what would be accepted currently. The Agency/CDRH recommends that the exhaustiveness of extraction be determined through gravimetric analysis of the non-volatile residue. However, these studies were conducted in 2010/2011 and were accepted by the Agency in DMF (b) (4). It is the opinion of the reviewer that this application's determination of exhaustiveness is more representative than NVR analysis as extractable compounds are identified and monitored for increases in concentration. Oligomeric substances in turn can be identified and monitored to determine when the device begins to degrade and be dissolved, providing the approximate timepoint for device degradation.

(b) (4)



Reviewer comment: The extraction analysis is sufficient to support TRA.

LC/MS

(b) (4)



(b) (4)



Reviewer comment: The extraction analysis is sufficient to support TRA.

ICP/MS & ICP/OES

(b) (4)



Reviewer comment: Extractions were performed consistent with the E&L study based on GC/MS and LC/MS methodologies. The applicant doesn't evaluate elements in the ICH Q3D(R1) Guideline published in 2019 as the analysis was conducted in 2010 as previously accepted by the Agency. The applicant has provided language stating the device is identical to that of that provided

in DMF (b) (4) The reporting limit for the elements as reported is sufficiently low to support TRA.

7. Recommended Deficiencies

No deficiencies to submit.

8. Recommendation

Completed No Deficiencies (CND)

9. Additional Comments

(b) (4)

Reviewer comment: All test reports have been received and reviewed. No outstanding requests.

10. Signed

John S. Bender -S
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John S. Bender, Ph.D.

Chemist

Respiratory Devices

THT1C3/DHT1C/OHT1/OPEQ/CDRH/FDA

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 5, 2021
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214324
Product Name and Strength:	Tyvaso DPI (treprostinil) inhalation powder, 16 mcg, 32 mcg, 48 mcg, and 64 mcg
Applicant/Sponsor Name:	United Therapeutics Corp.
OSE RCM #:	2021-795-1
DMEPA 2 Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA 2 Team Leader:	Colleen Little, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on October 1, 2021 for Tyvaso DPI. The Division of Cardiology and Nephrology (DCN) requested that we review the revised carton labeling for Tyvaso DPI (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Oguntimein O. Human Factors Results and Label and Labeling Review for Tyvaso DPI (NDA 214324). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 SEP 17. RCM No.: 2021-794 2021-795.

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HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 17, 2021
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214324
Product Type:	Combination Product (Drug-Device)
Drug Constituent Name and Strength	Tyvaso DPI ^a (treprostinil) inhalation powder, 16 mcg, 32 mcg, 48 mcg, and 64 mcg
Device Constituent:	Dry powder inhaler (DPI)
Rx or OTC:	Rx
Applicant/Sponsor Name:	United Therapeutics Corporation (UTC)
Submission Date:	April 16, 2021; June 21, 2021; and August 13, 2021
OSE RCM #:	2021-795 and 2020-796
DMEPA 2 Human Factors Specialist:	Murewa Oguntimein, PhD, MHS, CHES, CPH
DMEPA 2 Safety Evaluator (Labeling):	Ebony Whaley, PharmD, BCPPS
DMEPA 2 Team Lead (Acting):	Colleen Little, PharmD
DMEPA 2 Associate Director for Human Factors (Acting):	Lolita White, PharmD
DMEPA 2 Associate Director for Nomenclature and Labeling:	Chi-Ming (Alice) Tu, PharmD, BCPS

^a The proposed proprietary name, Tyvaso DPI, was found conditionally acceptable on June 17, 2021.

1. REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under NDA 214324 for Tyvaso DPI (treprostinil) inhalation powder.

1.1 BACKGROUND

Tyvaso (treprostinil) inhalation solution, for oral inhalation use is currently marketed under NDA 022387. Sterile solution for oral inhalation is supplied in 1.74 mg/2.9 mL ampules, packaged as 4 ampules in a foil pouch. Tyvaso is intended for use with the Tyvaso Inhalation System.

UTC now seeks approval for a different dosage form, Tyvaso DPI (treprostinil) inhalation powder under NDA 214324.

1.2 PRODUCT DESCRIPTION

Tyvaso DPI (treprostinil) inhalation powder is supplied in four strengths: 16 mcg, 32 mcg, 48 mcg, or 64 mcg of treprostinil in disposable one time use plastic cartridges provided in a blister strip configuration.

This is a combination product with a proposed dry powder inhaler device constituent part that is intended to treat pulmonary arterial hypertension (PAH; WHO Group 1) and pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. See Appendix A.

1.3 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On April 23, 2020, United Therapeutics Corporation (UTC) submitted their HF validation study protocol under IND 134582. Our review of the HF validation study protocol identified several areas of concern. On June 17, 2020, we communicated our recommendations to UTC in a HF Validation Study Protocol Advice Letter.^b

On April 16, 2021, UTC submitted the results of the HF validation study for Tyvaso DPI (treprostinil) inhalation powder under NDA 214324, which is the subject of this review.

^b Manitsipitkul, W. Human Factors Validation Study Advice for IND 134582. (MD): FDA, CDER, DMEPA (US); 17 JUN 2020. Available from: https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af805714fa&_afRedirect=1531342166332623

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed, and our analysis to determine if the results demonstrate that the user interface has been optimized support the safe and effective use of the proposed product.

3.1 SUMMARY OF STUDY DESIGN

Table 2 presents a summary of the HF validation study design.

Table 2. Study Methodology for Human Factors (HF) Validation Study			
Study Design Elements	Details		
Participants	pulmonary arterial hypertension (PAH) patients, pulmonary hypertension associated with interstitial lung disease (PH-ILD) patients; WHO Group 3 pulmonary hypertension- chronic obstructive pulmonary disease (PH-COPD) patients.		
	Group	Inhaler Experience	
		Experienced	Naïve
		Total	
		PAH patients	7
		PH-COPD patients	8
		10	1
		17	9

		PH-ILD patients	0	4	4
		Total	15	15	30
Training	Training was provided to the 30 participants with a 24-hour decay period				
Test Environment	The test room was set up to simulate a home environment.				
Sequence of Study	Training 24-hour decay Simulated Use Scenario Root Cause Analysis (RCA) Knowledge Assessment RCA Instructions for Use (IFU) feedback				

4. DISCUSSION

4.1 METHODOLOGY

Our review of the HF validation study methodology finds that UTC did not include an untrained user group as we recommended in our HF Validation Study Protocol Advice Letter.^c UTC provided a rationale for not including an untrained user group in their HF validation study. UTC stated that Tyvaso DPI is considered a specialty drug that will be dispensed to patients via UTC's two specialty pharmacies (b) (4) and (b) (4). UTC also stated that all users will receive training from the specialty pharmacy nurse trainer, who will sign-off certifying that the patient can receive a prescription for Tyvaso DPI only after the user has demonstrated proper use by administering a dose and completing all the critical tasks shown during the training. Furthermore, UTC stated that the training program validated in the HF study is representative of the planned commercial training program. The commercial nurse trainers from UTC's two specialty pharmacies will use a checklist similar to the training checklist used in the HF study to assess post-training competency in the commercial setting. Finally, UTC stated that to ensure that every user will routinely receive the same training, UTC will employ a team of nurses called the Clinical Product Training Team that train the two Specialty Pharmacies (b) (4) and (b) (4) on proper device usage and user training, using a similar checklist based on the HF

^c Manitpisitkul, W. Human Factors Validation Study Advice for IND 134582. (MD): FDA, CDER, DMEPA (US); 17 JUN 2020. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805714fa&_afRedirect=1531342166332623

training checklist. Per UTC, the use of this checklist ensures that regardless of which specialty pharmacy or nurse is utilized, each user is trained on the same criteria.

Our review finds that based on the above considerations, we accept the HF validation study methodology, and we agree with UTC that the controls outlined above will ensure that routine and consistent training will be provided to every intended user of Tyvaso DPI and thus we find that the inclusion of only trained participants in the HF validation study is representative of real world-use.

4.2 ANALYSIS OF CRITICAL TASK ERRORS

The HF validation studies showed four use errors (e.g., failures, difficulties, and close calls) with the following critical tasks listed below:

- Identify the expiration date on the titration kit (n=1, one participant who experienced use difficulty in locating and reading the expiration date on the titration kit had blurry vision from Graves' Disease).
- Using blister cards after 2 weeks if stored at room temperature (n=1, one participant demonstrated use difficulty when locating the proper storage of the blister cards but ultimately located the information in the IFU with no identified subjective feedback for suggested improvements).
- Keep inhaler level (n=1)
 - o One participant experienced a use error by holding the inhaler upside-down after loading it. Based on the URR, holding the inhaler upside-down may result in underdose/partial or reduced or no symptom relief. The participant provided subjective feedback and stated she likes to do things fast and must have forgotten between yesterday and today how to hold the DPI. This participant did not point to anything in the user interface to revise to prevent this from happening in the future.
- Cleaning the inhaler (n=1, one participant experienced use difficulty in finding the cleaning information in the IFU but ultimately located the information.)

After reviewing the available participants' subjective feedback and the Applicant's root cause analysis, our assessment of these user errors finds that the residual risks are acceptable, and we have no recommendations at this time.

4.3 LABELS AND LABELING

Tables 3 and 4 below include the identified medication error issues with the submitted labels and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 3: Identified Issues and Recommendations for Division of Cardiology and Nephrology			
	Identified Issue	Rationale for Concern	Recommendation
Full Prescribing Information (FPI): Highlights			
1.	The package type term “(b) (4)” is used to describe the product (i.e., “(b) (4) cartridges”).	“(b) (4)” is not considered an appropriate package type term. ^d	We defer to the Office of Pharmaceutical Quality (OPQ) to determine if it is appropriate to revise the package type term, “(b) (4)” to “single-dose”.
Full Prescribing Information: Section 2 Dosage and Administration			
2.	The location of the missed dose statement (“If a scheduled treatment session is missed, therapy should be resumed as soon as possible at the usual dose) can be improved.	The missed dose statement appears (b) (4) which might lead to the missed dose information being overlooked by readers.	Consider relocating the statement to appear above the “Dosage for Transition from Tyvaso (treprostinil) Inhalation Solution” section.
3.	Section 2 Dosage and Administration does not provide detailed information regarding administration of doses	Lack of information regarding doses higher than 64 mcg per treatment session may lead to wrong dose medication errors. Additionally, without	Consider revising Section 2 Dosage and Administration to include more detailed information regarding doses higher than 64 mcg per treatment session.

^d Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2018. Available from: <https://www.fda.gov/media/117883/download>.

	higher than 64 mcg per treatment session.	this information, certain product presentations may appear incongruent with the dosing information (i.e., the maintenance kit containing 32 mcg and 48 mcg cartridges allows for an 80 mcg dose; however, an 80 mcg dose is not listed in the PI).	
Full Prescribing Information: Section 3 Dosage Forms and Strengths			
4.	Refer to FPI Highlights recommendation #1 and consider revising accordingly.		
Full Prescribing Information: Section 16 How Supplied/ Storage and Handling			
5.	Refer to FPI Highlights recommendation #1 and consider revising accordingly.		
6.	In the table for Tyvaso DPI product configurations, the “Number of Cartridges” column header can be improved to better convey the contents of the column. Additionally, the formatting of the information can be improved for clarity.	Confusion regarding the product configurations and contents might result in confusion and risk of product selection or wrong strength errors.	Consider revising the column header “(b) (4)” to “Number of Cartridges and Strength”. Additionally, consider revising the formatting of the information from “(b) (4)” to “XX cartridges, each containing XX mcg per cartridge”.
7.	The storage information for the DPI cartridges can be improved for clarity.	Unclear storage information might result in confusion and	We recommend the blister card storage information is revised to tabular format as proposed below:

		risk of deteriorated drug medication errors.	Storage			
			Tyvaso DPI presentation	Refrigerated storage 2°C to 8°C (36°F to 46°F)	Room temperature storage 20°C to 25°C (68°F to 77°F), excursions permitted 15°C to 30°C (59°F to 86°F)	
			Sealed (Unopened) Blister Cards or Strips	May be stored until the expiration date printed on the blisters	Must be used within 5 weeks	
			Opened Strips	Do not put a blister card or strip back into the refrigerator after being opened or stored at room temperature.	Must be used within 3 days	

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Table 4: Identified Issues and Recommendations for United Therapeutics Corporation (UTC) (entire table to be conveyed to Applicant)

	Identified Issue	Rationale for Concern	Recommendation
Carton Labeling (Institutional Kit, Maintenance Kit, Titration Kit)			
1.	The artwork used to present the proprietary name “Tyvaso DPI” appears separated by the “(b) (4)” graphic feature, and the smaller font size and different color used to present the modifier “DPI”.	We are concerned that the artwork might lead users to misinterpret the proprietary name as “(b) (4)” or omit the modifier. Per 21 CFR 201.10(a), the ingredient information required by section 502(e) of the Federal Food, Drug, and Cosmetic Act shall appear together, without any intervening written, printed, or graphic matter, except the proprietary names of ingredients.	Revise the artwork so that the proprietary name reads as “Tyvaso DPI”.
2.	The strength presentation does not specify that the designated strength (xx mcg) is per single unit (cartridge).	Failure to clearly express the product strength in (XX mcg) per single unit (cartridge) may lead to wrong dose errors.	Revise the strength presentation from “(b) (4)” to “xx mcg per cartridge” to make it clear that the designated strength is per unit. We recommend this revision to mitigate the risk of confusion regarding the amount of product contained in a single unit as compared to the total contents of the entire blister card.
3.	The prominence of the product strength can be improved.	We acknowledge the product strength appears in the (b) (4) of the principal display panel	Consider relocating the product strength to appear in close proximity (e.g., directly

		(PDP). However, we are concerned that it may be overlooked because it does not appear in close proximity to other key product identifying information on the PDP such as the proprietary name, established name, and dosage form.	below) the established name and dosage form.
4.	The net quantity (i.e., number of cartridges in the carton) as displayed on the PDP is unclear. For example, the 48 mcg maintenance kit PDP states, “(b) (4)”; however, it is unclear if the number “(b) (4)” refers to the number of cartridges or a product strength (i.e., (b) (4)).	We are concerned that as presented on the PDP, there is risk of numerical confusion between the net quantity and strength. For example, users may not be able to differentiate between the net quantity and strength which might confuse users regarding the number of cartridges in the carton and might lead to dosing errors.	Revise the net quantity on the PDP to be displayed with alphabetical characters instead of numerical characters to differentiate from the product strength. For example: - For the 48 mcg maintenance kit net quantity statement, consider revising “(b) (4)” to “Kit contains (b) (4) cartridges, each containing 48 mcg per cartridge” - For the 16 mcg-32 mcg-48 mcg titration kit net quantity statement, consider revising (b) (4) to “Kit contains (b) (4) cartridges, each containing 16 mcg per cartridge”; “(b) (4) cartridges, each containing 32 mcg per cartridge”; “(b) (4) cartridges, each containing 48 mcg per cartridge”

5.	The “Usual Dose” statement is not in the correct format.	The “Usual Dose” statement should be aligned with the Prescribing Information.	To ensure consistency with the Prescribing Information, revise the statement (b) (4) to read “Recommended Dosage: See Prescribing Information. Include the statement, “See Instructions for Use for administration information.” Below the “Usual Dose” statement.
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5. CONCLUSION AND RECOMMENDATIONS

The results of the human factors (HF) validation study results identified use errors with critical tasks, however, our review finds the residual risks are acceptable for these use errors. Additionally, our evaluation of the proposed packaging, labels and labeling identified areas of vulnerability that may lead to medication errors. However, these recommendations can be implemented without the submission of additional human factors. We provide recommendations that we advise are implemented prior to approval. Above, we have provided recommendations in Table 3 for the Division and Table 4 for the Applicant. We ask that the Division convey Table 4 in its entirety to the Applicant so that recommendations are implemented prior to approval of this NDA.

5.1 RECOMMENDATIONS FOR THE UNITED THERAPEUTICS CORPORATION

Our evaluation of the proposed Tyvaso DPI packaging, labels and labeling identified areas of vulnerability that may lead to medication errors. We provide these recommendations in Table 4 and we recommend that you implement these recommendations and submit your revised labels and labeling prior to approval of this NDA. We have determined that at this time, you may implement these revisions without submitting additional human factors validation data for Agency review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Tyvaso DPI that UTC submitted on April 16, 2021.

Table 5. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	prostacyclin vasodilator
Active Ingredient (Drug or Biologic)	treprostinil
Indication	for treatment of pulmonary arterial hypertension (PAH; WHO Group 1) and pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability.
Route of Administration	oral inhalation
Dosage Form	inhalation powder
Strength	16 mcg, 32 mcg, 48 mcg, and 64 mcg
Dose and Frequency	Tyvaso DPI is dosed in 4 separate, equally spaced treatment sessions per day, during waking hours. The treatment sessions should be approximately 4 hours apart. (b) (4) . If the prescribed dose is higher than 64 mcg per treatment session, more than 1 cartridge will be needed per session. The cartridges can be used in any order, regardless of cartridge strength. <i>Initial Dosage:</i> Tyvaso DPI therapy should begin with one 16 mcg cartridge per treatment session, 4 times daily. <i>Maintenance Dosage:</i> Dosage should be increased by an additional 16 mcg per treatment session at approximately 1- to 2-week intervals; the appropriate dosage (cartridge) strength should be selected for each up-titration. If the prescribed dose is higher than 64 mcg per treatment session, more than 1 cartridge will be needed per session. The cartridges can be used in any order, regardless of cartridge strength.
How Supplied	Tyvaso DPI (treprostinil) inhalation powder is available as 16 mcg, 32 mcg, 48 mcg, or 64 mcg of treprostinil in plastic cartridges with

	approximate fill weights of 1.6 mg, 3.2 mg, 4.8 mg, or 6.4 mg of Tyvaso DPI, respectively. Four cartridges are contained in a single cavity of a blister strip. Each card contains 7 blister strips separated by perforations for a total of 28 cartridges. For convenience, the perforation allows users to remove a single strip containing 4 cartridges. The cartridges are color-coded, purple for 16 mcg, dark blue for 32 mcg, light blue for 48 mcg, and light green for 64 mcg. Each cartridge is marked with “Tyvaso DPI” and the corresponding dosage strength of “16 mcg”, “32 mcg”, “48 mcg”, or “64 mcg”. Tyvaso DPI is available in the following configurations:																																							
	<table><tr><th colspan="2"></th><th colspan="2">Kit Contents</th></tr><tr><th>NDC</th><th>Description</th><th>(b) (4)</th><th>Number of Inhalers</th></tr><tr><td>66302-600-02</td><td>Tyvaso DPI (treprostinil)</td><td rowspan="15"></td><td>5</td></tr><tr><td>66302-610-02</td><td>Inhalation Powder Titration Kit</td><td>5</td></tr><tr><td>66302-616-03</td><td rowspan="5">Tyvaso DPI (treprostinil) Inhalation Powder Maintenance Kit</td><td>5</td></tr><tr><td>66302-632-03</td><td>5</td></tr><tr><td>66302-648-03</td><td>5</td></tr><tr><td>66302-664-03</td><td>5</td></tr><tr><td>66302-620-03</td><td>5</td></tr><tr><td>66302-616-04</td><td rowspan="5">Tyvaso DPI (treprostinil) Inhalation Powder Institutional Kit</td><td>2</td></tr><tr><td>66302-632-04</td><td>2</td></tr><tr><td>66302-648-04</td><td>2</td></tr><tr><td>66302-664-04</td><td>2</td></tr><tr><td>66302-(b) (4)-04</td><td>2</td></tr></table>					Kit Contents		NDC	Description	(b) (4)	Number of Inhalers	66302-600-02	Tyvaso DPI (treprostinil)		5	66302-610-02	Inhalation Powder Titration Kit	5	66302-616-03	Tyvaso DPI (treprostinil) Inhalation Powder Maintenance Kit	5	66302-632-03	5	66302-648-03	5	66302-664-03	5	66302-620-03	5	66302-616-04	Tyvaso DPI (treprostinil) Inhalation Powder Institutional Kit	2	66302-632-04	2	66302-648-04	2	66302-664-04	2	66302-(b) (4)-04	2
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66302-664-04			2																																					
66302-(b) (4)-04			2																																					
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	<table> <tr> <td>Sealed (Unopened) Blister Cards and Strips</td><td>May be stored until the Expiration Date printed on the blisters^a</td></tr> </table> ^a If a blister card or strip is not refrigerated, the contents must be used within 5 weeks. In Use: Room Temperature Storage 20°C to 25°C (68°F to 77°F), excursions permitted 15°C to 30°C (59°F to 86°F) <table> <tr> <td>Sealed (Unopened) Blister Cards and Strips</td><td>Must be used within 5 weeks</td></tr> <tr> <td>Opened Strips</td><td>Must be used within 3 days</td></tr> </table> Do not put a blister card or strip back into the refrigerator after being opened or stored at room temperature. Inhaler Storage: Store at 2°C to 25°C (36°F to 77°F); excursions permitted. The Tyvaso DPI Inhaler may be stored refrigerated but should be at room temperature for 10 minutes before use. The inhaler can be used for up to 7 days from the date of first use. After 7 days of use, the inhaler must be discarded and replaced with a new inhaler.	Sealed (Unopened) Blister Cards and Strips	May be stored until the Expiration Date printed on the blisters ^a	Sealed (Unopened) Blister Cards and Strips	Must be used within 5 weeks	Opened Strips	Must be used within 3 days
Sealed (Unopened) Blister Cards and Strips	May be stored until the Expiration Date printed on the blisters ^a						
Sealed (Unopened) Blister Cards and Strips	Must be used within 5 weeks						
Opened Strips	Must be used within 3 days						
Container Closure/Device Constituent	Each Kit consists of the inhaler, cartridges, and IFU (b) (4)						
Intended Users	Patients with PAH and PH-ILD						
Intended Use Environment	Home, office, healthcare setting, or other similar environment						

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On April 15, 2020, we searched the L: drive and AIMS using the terms, IND 134582, and NDA 214324 to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified one previous review^e and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in the HF results report. See Appendix D.

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:

<\\CDSESUB1\evsprod\nda214324\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pah\5354-other-stud-rep\tyvdpi-hf-val\tyvdpi-hf-val-hf-validation-report-2.pdf>

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On June 21, 2021, we issued an Information Request (IR) to request the following:

- UTC's training scripts
- Confirm that the training program validated in your HF study is representative of the training program for your commercial product should your product be approved.
- Provide detailed information of the criteria for patient "sign-off"

UTC provided an acceptable response on June 23, 2021, that can be accessible in EDR via:

<\\CDSESUB1\evsprod\nda214324\0006\m1\us\12-cover-letters\cover.pdf>

^e Kalonia. J. Human Factors Validation Study Protocol Review for treprostinil inhalation powder IND 134582. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 11. RCM No.: 2020-846.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^f along with postmarket medication error data, we reviewed the following Tyvaso labels and labeling submitted by UTC.

- Container labels (Blister Strips- Blister layout, Titration slot tray and Maintenance slot trays) received on April 16, 2021 and August 13, 2021
- Carton labeling (Institutional Kits) received on August 13, 2021
- Carton labeling (Titration Kits) received on August 13, 2021
- Carton labeling (Maintenance Kits) received on August 13, 2021
- Instructions for Use received on April 16, 2021. Available from <\\CDSESUB1\evsprod\nda214324\0002\m1\us\114-labeling\draft\labeling\draft-ifu-clean-pdf.pdf>
- Prescribing Information (Image not shown) received on August 13, 2021. Available from <\\CDSESUB1\evsprod\nda214324\0008\m1\us\114-labeling\draft\labeling\draft-pi-clean-pdf.pdf>

F.2 Label and Labeling Images

Container Labels

Blister Strip graphics



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

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: September 15, 2021

To: Brian Cooney, MS, PSM
Regulatory Project Manager
Division of Cardiology and Nephrology (DCN)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Morgan Walker, PharmD, MBA, CPH
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Ruth Mayrosh, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

David Foss, Pharm. D., MPH, BCPS, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Instructions for Use (IFU)

Drug Name (established name): TYVASO DPI (treprostinil)

Dosage Form and Route: inhalation powder, for oral inhalation use

Application Type/Number: NDA 214324

Applicant: United Therapeutics Corporation

1 INTRODUCTION

On April 16, 2021, United Therapeutics Corporation submitted for the Agency's review an original New Drug Application (NDA) 214324 for TYVASO DPI (treprostinil) inhalation powder to treat pulmonary arterial hypertension (PAH) and PAH associated with interstitial lung disease to improve exercise ability. This product is a drug-device combination comprised of single use cartridges containing a dry powder formulation of Treprostinil and a reusable dry powder inhaler. It is a change in dosage form from NDA 022387 Tyvaso inhalation solution to a dry powder for oral inhalation.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Cardiology and Nephrology (DCN) on June 8, 2021, for DMPP and OPDP to review the Applicant's proposed Instructions for Use (IFU) for TYVASO DPI (treprostinil) inhalation powder.

2 MATERIAL REVIEWED

- Draft TYVASO DPI (treprostinil) inhalation powder IFU received on April 16, 2021, and received by DMPP and OPDP on September 2, 2021.
- Draft TYVASO DPI (treprostinil) inhalation powder Prescribing Information (PI) received on April 16, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 2, 2021.
- Draft TYVASO DPI (treprostinil) inhalation powder HFS-IFU DMPP review dated May 4, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the IFU we:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

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

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

Memorandum

Date: September 8, 2021

To: Mitchell Psotka, M.D.
Division of Cardiovascular and Renal Products (DCRP)

Michael Monteleone, Associate Director for Labeling, (DCRP)

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for TYVASO DPI (treprostinil) inhalation powder, for oral inhalation use

NDA: 214324

In response to DCRP's consult request dated June 8, 2021, OPDP has reviewed the proposed product labeling (PI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for Tyvaso DPI.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DCRP on September 2, 2021, and are provided below.

OPDP comments on the proposed IFU will be sent under separate cover, either as a combined OPDP and Division of Medical Policy Programs (DMPP) review or a separate OPDP review.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room April 16, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov

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

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MEMORANDUM

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

DATE: 6/24/2021

TO: Division of Cardiology and Nephrology (DCN)
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 214324

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspections are not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

PPD Development, L.P.: The Office of Regulatory Affairs (ORA) inspected the site in November 2018, which falls within the surveillance interval. The inspection was conducted under the following submission: NDA 211225. The final classification for the inspection was No Action Indicated (NAI).

(b) (4) OSIS inspected the site in (b) (4), which falls within the surveillance interval. The inspection was conducted under the following submissions: (b) (4)

The final classification for the inspection was Voluntary Action Indicated (VAI) for the following observations:

- (b) (4)

After receiving a written response from the site, OSIS determined that the data from the audited studies were reliable to support a regulatory decision. ([Final OSIS EIR Review - \(b\) \(4\) Inspection](#))

Therefore, based on the rationale provided above, inspections are not warranted at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	PPD Development, L.P.	7551 Metro Center Drive, Suite 200, Austin, TX

Analytical

(b) (4)

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/s/

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