CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214324Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 214324
TYVASO (Treprostinil) Dry Powder Inhaler, 16 mcg, 32 mcg, 48 mcg, 64 mcg

Integrated Quality Review # 2

Recommendation: Approval

Drug Name/Dosage Form	TYVASO (Treprostinil) DPI™ / Dry Powder Inhaler
Strength	16 mcg, 32 mcg, 48 mcg, 64 mcg
Route of Administration	Inhalation
Rx/OTC Dispensed	Rx
Indication	(b) (4)
Applicant	United Therapeutics Corp.
Submissions (s) Reviewed	NDA 214324 (Class I Resubmission)

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Daniel Jansen	ONDP/DNDAPI/NDB3
Drug Product/Environmental Assessment (EA)	Akm Khairuzzaman	ONDP/DNDPIII/NDPB5
Process and Facility	Alexander Gontcharov	OPQ/OPMA/DPMAIII/PMB7
Biopharmaceutics	Parnali Chatterjee	ONDP/DB/BB3
RBPM	Grafton Adams	OPRO/ DRBPMI
Application Technical Lead (ATL)	Akm Khairuzzaman	ONDP/DNDPIII/NDPB5

Link for Integrated Quality Review # 1:
https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8061de0c&showAsPdf=true

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls (CMC) perspective, NDA 214324 is recommended for **approval**. As part of this action, 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. The drug product in unopened blister cards/strips is permitted to be stored up to 5 weeks at room temperature.

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

None.

II. Background, and Quality Assessment Summary

This is the second integrated quality assessment for this NDA, which specifically addresses the facility related issues that were communicated to the Applicant, United Therapeutics Corporation via a complete response (CR) letter dated 10/15/2021. The Agency issued a CR because of an official action indicated (OAI) classification for the drug substance testing facility, (b) (4) On 12/23/2021, the Applicant resubmitted the NDA (class I resubmission). The resubmitted NDA indicated withdrawal of the (b) (4) and its replacement with two alternate drug substance testing facilities, namely, (b) (4) (b) (4) and United Therapeutics Corporation, Silver Spring, MD. 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 office of Pharmaceutical Manufacturing Assessment (OPMA/OPQ) has recommended approval for these newly listed facilities. Therefore, the complete response issues are now adequately resolved from quality perspective and the NDA is now recommended for approval.

A. Drug Substance Quality Summary

The revised information regarding the drug substance testing provided in this NDA resubmission is found to be adequate by the drug substance reviewer (please see link below). The updated analytical testing information and batch data from the new (b) (4) content testing site, (b) (4) is also found to be acceptable. Stability data support a retest period of (b) (4) months for the Treprostinil drug substance when stored in (b) (4). For details, refer to the drug substance review chapters via the links provided below:
Review # 1: https://panorama.fda.gov/document/view?ID=60faf56900105cfd102fb56e641a3915
Review # 2: NDA 214324 Treprostinil Resub DJJ review (fda.gov)

B.1. Product Design, and Release Specification: There is no change in product design and release specification. For details, refer to the first integrated quality assessment via the link provided on page 1of this review.

B.2. Manufacturing: The details of manufacturing process and its controls are provided in DMF # (b) (4) The DMF has been reviewed and found to be adequate to support this NDA. Please refer to the drug product manufacturing review chapter via the link provided below:
https://panorama.fda.gov/task/view?ID=613f5211001f11f930b4b0dac4e0d7c8

B.3. Microbiological Aspects: Please refer to the first integrated quality assessment via the link provided below:
https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8061de0c&showAsPdf=true

B.4. Biopharmaceutics Aspects: Not relevant for this drug product. Please refer to the biopharmaceutics memo via the link provided below.
https://panorama.fda.gov/document/view?ID=612cfae70007d87740434814e7a82037

B.5. Container Closure System: There is no change in the container closure system. Please refer to the first integrated quality assessment via the link provided below:
https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8061de0c&showAsPdf=true

B.6. Product Stability, Expiration Date & Storage Conditions. The Applicant's proposed shelf life of 18 months with recommended storage condition of **2°C to 8°C (36°F to 46°F)** is acceptable. The drug product in unopened blister cards/strips is permitted to be stored up to 5 weeks at room temperature. . For details, refer to the first integrated quality assessment via the link provided below:
https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8061de0c&showAsPdf=true

C. Assessment of Manufacturing Facilities: As indicated below (Panorama facility status: Overall Manufacturing Inspection Recommendation (fda.gov)), the office of Pharmaceutical Manufacturing Assessment (OPMA) has recommended approval for all the facilities listed in this NDA resubmission..

(b) (4)

The details of facility review for this NDA resubmission can be found via the links provided below:
Review # 1: https://panorama.fda.gov/document/view?ID=614a71cd00f15ea352c925622ae847ff
Review # 2 (NDA-resubmission):
https://panorama.fda.gov/task/view?ID=61ddbfb20013e823a019fbe5aa7bc463

D. The applicant has claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(b) on the basis that no extraordinary circumstances exist under 21 CFR 25.15(d) that would warrant preparation of an environmental assessment. The applicant's claim of categorical exclusion is acceptable.

E. OPQ's all labeling recommendations are reflected in the most recent version of the product labeling.

OVERALL ASSESSMENT AND SIGNATURES

Application Technical Lead (ATL) Assessment and Signature:

Based on integrated quality review by the Office of Pharmaceutical Quality (OPQ), manufacturing facilities-related deficiencies are now adequately resolved. Therefore, from an OPQ perspective, this NDA is recommended for **approval**.

Akm Khairuzzaman, Ph.D.
Application Technical Lead (ATL)
ONDP/DNDPIII/NDPB5

Akm Khairuzzaman -S

Digitally signed by Akm Khairuzzaman -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000423292, cn=Akm Khairuzzaman -S
Date: 2022.01.31 08:03:50 -05'00'

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

/s/

AKM KHAIRUZZAMAN
01/31/2022 08:19:37 AM
OPQ Team Recommends an Approval for this NDA

MOHAN K SAPRU
01/31/2022 10:33:54 AM

NDA 214324
TYVASO (Treprostinil) Dry Powder Inhaler, 16 mcg, 32 mcg, 48 mcg, 64 mcg

Integrated Quality Review
Recommendation: A Complete Response (CR)

Drug Name/Dosage Form	TYVASO (Treprostinil) DPI™ / Dry Powder Inhaler
Strength	16 mcg, 32 mcg, 48 mcg, 64 mcg
Route of Administration	Inhalation
Rx/OTC Dispensed	Rx
Applicant	United Therapeutics Corp.
Submissions (s) Reviewed	NDA 214324, and all the submitted CMC amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Daniel Jansen	ONDP/DNDAPI/NDB3
Drug Product/Environmental Assessment (EA)	Akm Khairuzzaman	ONDP/DNDPIII/NDPB5
Process and Facility	Alexander Gontcharov	OPQ/OPMA/DPMAIII/PMB7
Biopharmaceutics	Parnali Chatterjee	ONDP/DB/BB3
RBPM	Grafton Adams	OPRO/ DRBPMI
Application Technical Lead (ATL)	Akm Khairuzzaman	ONDP/DNDPIII/NDPB5

Quality Review Data Sheet

DMFs

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE OF REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate	9/15/2021	Reviews are in Panorama submitted by different OPQ sub-offices

Other Documents:

Type B Pre NDA written responses, dated November 19, 2020
Type C meeting minutes, dated December 17, 2019
Type C meeting minutes preliminary comments, dated January 06, 2019
Type B Pre-NDA meeting written response, dated July 28, 2017

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on integrated quality review by the Office of Pharmaceutical Quality (OPQ), manufacturing facilities-related deficiencies remain currently unresolved because of an official action indicated (OAI) for the drug substance testing facility, [redacted] (b) (4) ([redacted] (b) (4) resulting in 'withhold' recommendation for the facility. Therefore, from an OPQ perspective, this NDA is not deemed ready for approval in its present form until the above-mentioned facility related issue is resolved. As such, OPQ recommends a Complete Response (CR) action from a product quality perspective.

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

None.

II. Background, and Quality Assessment Summary

The applicant, United Therapeutics Corporation, has sought U.S. marketing approval for TYVASO (Treprostinil) Dry Powder Inhaler in accordance with Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act. Treprostinil is a prostacyclin analogue. Its major pharmacologic actions are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. The drug product is a drug-device combination product which is comprised of single-use cartridges containing a dry powder formulation of treprostinil inhalation powder (Tyvaso DPI™) at 16, 32, 48, or 64 mcg of treprostinil per cartridge and a small, portable, reusable, breath-powered, dry powder inhaler. This combination product is a change in dosage form for treprostinil from a solution for oral inhalation (Tyvaso® [treprostinil] Inhalation Solution, NDA 022387) to a dry powder for oral inhalation. All CMC information on this new drug product formulation of treprostinil is referenced to DMF (# [redacted] (b) (4) The DMF has been reviewed by different disciplines within the Office of Pharmaceutical Quality (OPQ) and found to be acceptable. The proposed control strategies for the drug product manufacturing are adequate to ensure consistent drug product quality regarding identity, assay, purity, dissolution, content uniformity, [redacted] (b) (4), microbial content, and stability. The proposed 18-month shelf life is supported by sufficient stability data and found to be acceptable. While all of the listed facilities were found to be acceptable, note that one of the facilities (drug substance testing laboratory) is currently on "withhold" status.

A. Drug Substance Quality Summary

Treprostinil is a small molecule and has been well characterized using state-of the-art methods with regard to its structure and physicochemical characteristics. The drug substance reviewer concluded that the manufacturing process of the drug substance has been described in sufficient detail and the proposed specification is adequate. Analytical methods to control the quality of the drug substance are adequate. Stability data support retest of [redacted] (b) (4) months for the Treprostinil drug substance when

stored in [redacted] (b) (4) Please refer to the drug substance review chapter via the link provided below:
https://panorama.fda.gov/document/view?ID=60faf56900105cfd102fb56e641a3915

B.1. Product Design, and Release Specification:

The drug product is a drug-device combination product which is comprised of single-use cartridges containing a dry powder formulation of treprostinil inhalation powder (Tyvaso DPI™) at 16, 32, 48, or 64 mcg of treprostinil per cartridge and a small, portable, reusable, breath-powered, dry powder inhaler. All chemistry, manufacturing, and control (CMC) information on this new drug product formulation of treprostinil is referenced to DMF # [redacted] (b) (4) The DMF has been reviewed and found to be adequate to support this NDA. Please refer to the drug product review chapter via the link provided below:
https://panorama.fda.gov/document/view?ID=613f43d6001d52c212db4661928f7dea

B.2. Manufacturing: The manufacturing process and its controls information are provided in the DMF # [redacted] (b) (4) The DMF has been reviewed and found to be adequate to support this NDA. Please refer to the drug product manufacturing review chapter via the link provided below:
https://panorama.fda.gov/task/view?ID=613f5211001f11f930b4b0dac4e0d7c8

B.3. Microbiological Aspects: The drug product is adequately controlled for inclusion of microbiological testing in the drug product specification. Please refer to the microbiology review chapter (provided under the DMF # [redacted] (b) (4) via the link provided below:
https://panorama.fda.gov/task/view?ID=5bc95737005ecff95a53bdacbced50d2

B.4. Biopharmaceutics Aspects: Not relevant for this drug product. Please refer to the biopharmaceutics memo via the link provided below.
https://panorama.fda.gov/document/view?ID=612cfae70007d87740434814e7a82037

B.5. Container Closure System: Treprostinil Inhalation Powder is packed into a single dose cartridge cup and sealed by a lid. The cartridge cups and lids are made of [redacted] (b) (4) The filled cartridges are packaged into blisters [redacted] (b) (4) sealed with aluminum lid. Each blister card contains seven (7) blisters strips separated by perforations for a total of 28 cartridges. The cartridge cup containing the inhalation powder is inserted into the inhalation device prior to administration. [redacted] (b) (4) [redacted] (b) (4) The product stability data indicate suitability of the proposed container closure system for the intended use. All CMC information regarding the container closure system is provided under the DMF # [redacted] (b) (4) which is found to be adequate to support this NDA.

B.6. Product Stability, Expiration Date & Storage Conditions. The applicant provided data from stability studies from eight (8) registration batches stored in the intended commercial packaging under long-term conditions (5°C ± 3°C) for up to 12 months, and accelerated conditions (25°C ± 2°C/60% RH) for 6 months. Additional stability data including in-use stability and stress condition stability data were also provided. Note that all stability data and associated reports are provided in the DMF # [redacted] (b) (4) which has been found to be adequate to support this NDA. All these stability data indicate no changes in the drug product with respect to any of the quality attributes. Therefore,

the applicant's proposed shelf life of 18-month with recommended storage condition of 5°C is acceptable.

C. Assessment of Manufacturing Facilities: The office of Pharmaceutical Manufacturing Assessment (OPMA) has recommended a "Withhold" under the overall manufacturing recommendation for this NDA as follows (copied from Panorama facility status).

Note that only one particular facility listed above (i.e., (b) (4)) has OAI classification due to compliance issue. This particular facility is a testing laboratory for the drug substance. All other listed facilities are GMP compliant. The facility review can be found via the link provided below:
https://panorama.fda.gov/document/view?ID=614a71cd00f15ea352c925622ae847ff

D. The applicant has claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(b) on the basis that no extraordinary circumstances exist under 21 CFR 25.15(d) that would warrant preparation of an environmental assessment. The applicant's claim of categorical exclusion is acceptable.

E. OPQ's all labeling recommendations are reflected in the most recent version of the product labeling.

OVERALL ASSESSMENT AND SIGNATURES

Application Technical Lead (ATL) Assessment and Signature:

Based on integrated quality review by the Office of Pharmaceutical Quality (OPQ), manufacturing facilities-related deficiencies remain currently unresolved because of an official action indicated (OAI) classification for the drug substance testing facility, (b) (4) (b) (4)). Therefore, from an OPQ perspective, this NDA is not deemed ready for approval in its present form until the above-mentioned facility's OAI status is changed to GMP complaint. As such, OPQ recommends a Complete Response (CR) action from a product quality perspective along with the following CR deficiency.

CR Deficiency for the Applicant:

During a recent inspection of the (b) (4) facility ((b) (4) for this application, our field investigator conveyed deficiencies to the representative of the facility. As a result of this inspection, FDA has classified this facility as Official Action Indicated (OAI) on (b) (4) for drug CGMP. Satisfactory resolution of these deficiencies is required before this application may be approved.

Akm Khairuzzaman, Ph.D.
Application Technical Lead (ATL)
ONDP/DNDPIII/NDPB5

Akm Khairuzzaman -S

Digitally signed by Akm Khairuzzaman -S
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Date: 2021.10.14 10:39:54 -04'00'

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/s/

AKM KHAIRUZZAMAN
10/14/2021 10:46:50 AM
Updated IQA. A Complete Response (CR) is recommended from OPQ due to facility issue.

MOHAN K SAPRU
10/14/2021 10:52:38 AM

NDA 214324
TYVASO (Treprostinil) Dry Powder Inhaler, 16 mcg, 32 mcg, 48 mcg, 64 mcg

Integrated Quality Review
Recommendation: A Complete Response (CR)

Drug Name/Dosage Form	TYVASO (Treprostinil) DPI™ / Dry Powder Inhaler
Strength	16 mcg, 32 mcg, 48 mcg, 64 mcg
Route of Administration	Inhalation
Rx/OTC Dispensed	Rx
Applicant	United Therapeutics Corp.
Submissions (s) Reviewed	NDA 214324, and all the submitted CMC amendments

Quality Review Team

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Drug Substance	Daniel Jansen	ONDP/DNDAPI/NDB3
Drug Product/Environmental Assessment (EA)	Akm Khairuzzaman	ONDP/DNDPIII/NDPB5
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B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

None.

II. Background, and Quality Assessment Summary

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A. Drug Substance Quality Summary

Treprostinil is a small molecule and has been well characterized using state-of the-art methods with regard to its structure and physicochemical characteristics. The drug substance reviewer concluded that the manufacturing process of the drug substance has been described in sufficient detail and the proposed specification is adequate. Analytical methods to control the quality of the drug substance are adequate. Stability data support retest of [redacted] (b) (4) months for the Treprostinil drug substance when stored in [redacted] (b) (4)

B.1. Product Design, and Release Specification:

The drug product is a drug-device combination product which is comprised of single-use cartridges containing a dry powder formulation of treprostinil inhalation powder (Tyvaso DPI™) at 16, 32, 48, or 64 mcg of treprostinil per cartridge and a small, portable, reusable, breath-powered, dry powder inhaler. All chemistry, manufacturing, and control (CMC) information on this new drug product formulation of treprostinil is referenced to DMF # (b) (4) The DMF has been reviewed and found to be adequate to support this NDA. Pharmaceutical development studies adequately support the formulation design, including excipient selection and excipient levels. No human/animal-origin excipients are used in the formulation. The drug product contains the drug substance and other inactive ingredients namely, fumaryl diketopiperazine, (b) (4), (b) (4), (b) (4), (b) (4), and (b) (4). (b) (4) . Fumaryl diketopiperazine (FDKP) is a non-compendial excipient. and has been used at a (b) (4) level in another FDA approved drug product, Afrezza (BLA-022472). The drug product is manufactured by (b) (4). (b) (4) (b) (4) (b) (4)

The product release specification, involving testing of all the product critical quality attributes (CQAs), is adequate to ensure the consistent product quality such as appearance, identification, assay, related compound, uniformity of dosage unit, aerodynamic particle size distribution, uniformity of delivered dose, foreign particulate matter, (b) (4), and microbial limits. All analytical methods used are validated. A risk assessment regarding levels of elemental impurities in the drug product have been assessed and found to be acceptable. A risk assessment of (b) (4) contamination in Treprostinil Inhalation Powder was also conducted and the risk was found to be very low/negligible.

B.2. Manufacturing: The manufacturing process and its controls information including manufacturing facilities provided in the DMF # (b) (4) The manufacturing process utilizes (b) (4) (b) (4) (b) (4) The DMF was found to be adequate from manufacturing process and control perspective by the reviewer to support this NDA.

B.3. Microbiological Aspects: The drug product is adequately controlled for inclusion of microbiological testing in the drug product specification.

B.4. Biopharmaceutics Aspects: Not relevant for this drug product.

B.5. Container Closure System: Treprostinil Inhalation Powder is packed into a single dose cartridge cup and sealed by a lid. The cartridge cups and lids are made of (b) (4) The filled cartridges are packaged into blisters (b) (4) sealed with aluminum lid. Each blister card contains seven (7) blisters strips separated by perforations for a total of 28 cartridges. The cartridge

cup containing the inhalation powder is inserted into the inhalation device prior to administration. (b) (4) (b) (4) The product stability data indicate suitability of the proposed container closure system for the intended use. All CMC information regarding the container closure system is provided under the DMF # (b) (4) which is found to be adequate to support this NDA.

B.6. Product Stability, Expiration Date & Storage Conditions. The applicant provided data from stability studies from eight (8) registration batches stored in the intended commercial packaging under long-term conditions (5°C ± 3°C) for up to 12 months, and accelerated conditions (25°C ± 2°C/60% RH) for 6 months. Additional stability data including in-use stability and stress condition stability data were also provided. Note that all stability data and associated reports are provided in the DMF # (b) (4) which has been found to be adequate to support this NDA. All these stability data indicate no changes in the drug product with respect to any of the quality attributes. Therefore, the applicant's proposed shelf life of 18-month with recommended storage condition of 5°C is acceptable.

C. Assessment of Manufacturing Facilities: The office of Pharmaceutical Manufacturing Assessment (OPMA) has recommended a "Withhold" under the overall manufacturing recommendation for this NDA as follows (copied from Panorama facility status).

(b) (4)

Note that only one particular facility listed above (i.e., (b) (4)) has OAI classification due to compliance issue. This particular facility is a testing laboratory for the drug substance. All other listed facilities are GMP compliant.

D. The applicant has claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(b) on the basis that no extraordinary circumstances exist under 21 CFR 25.15(d) that would warrant preparation of an environmental assessment. The applicant's claim of categorical exclusion is acceptable.

E. OPQ's all labeling recommendations are reflected in the most recent version of the product labeling.

OVERALL ASSESSMENT AND SIGNATURES

Application Technical Lead (ATL) Assessment and Signature:

Based on integrated quality review by the Office of Pharmaceutical Quality (OPQ), manufacturing facilities-related deficiencies remain currently unresolved because of an official action indicated (OAI) classification for the drug substance testing facility, (b) (4) (b) (4)). Therefore, from an OPQ perspective, this NDA is not deemed ready for approval in its present form until the above-mentioned facility's OAI status is changed to GMP complaint. As such, OPQ recommends a Complete Response (CR) action from a product quality perspective along with the following CR deficiency.

CR Deficiency for the Applicant:

During a recent inspection of the (b) (4) *facility (* (b) (4) *for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.*

Akm Khairuzzaman, Ph.D.
Application Technical Lead (ATL)
ONDP/DNDPIII/NDPB5

Akm Khairuzzaman -S

Digitally signed by Akm Khairuzzaman -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000423292, cn=Akm Khairuzzaman -S
Date: 2021.09.30 11:39:37 -04'00'

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/s/

AKM KHAIRUZZAMAN
09/30/2021 11:45:28 AM
OPQ Team has recommended a Complete Response (CR) due to pending facility related issue

MOHAN K SAPRU
09/30/2021 11:48:14 AM

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Items	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	TYVASO DPI™	Acceptable
Established name(s)	Treprostinil inhalation powder for oral inhalation use	Acceptable
Route(s) of administration	oral inhalation	Acceptable
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Inhalation powder for oral inhalation use. 16 mcg, 32 mcg, 48 mcg, and 64 mcg	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	Acceptable
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Separate labeling/ package insert has been provided that includes step-by-step instruction (along with picture) on how to remove the drug filled cartridges from the blister pack and insert into the inhalation device prior to use. This is also subject to further review by the labeling reviewers.	Acceptable
Available dosage form(s)	Inhalation powder for oral inhalation use	Acceptable

Strength(s) in metric system	Not applicable	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Not applicable, not a salt	Acceptable

1.2.3 Section 11 (DESCRIPTION)

Items	**Information Provided in the NDA**	**Assessor's Comments**
DESCRIPTION section		
Proprietary and established name(s)	TYVASO DPI™ (treprostinil) inhalation powder, for oral inhalation use	Acceptable
Dosage form(s) and route(s) of administration	Inhalation powder, for oral inhalation use	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Not a salt (NA)	Acceptable
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Provided	Acceptable
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Not a parenteral product	Acceptable
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not Applicable	Acceptable
Statement of being sterile (if applicable)	Not a sterile product	Acceptable
Pharmacological/ therapeutic class	Prostacyclin mimetic	Acceptable
Chemical name, structural formula, molecular weight	Provided	Acceptable
If radioactive, statement of important nuclear characteristics.	Not Applicable	Acceptable
Other important chemical or	None	Acceptable

physical properties (such as pKa or pH)		
Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity	None present	Acceptable

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Items	**Information Provided in the NDA**	**Assessor’s Comments**
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Inhalation powder, for oral inhalation use	Acceptable.
Strength(s) in metric system	Not applicable	Acceptable
Available units (e.g., bottles of 100 tablets)	Each card contains 7 blister strips separated by perforations for a total of 28 cartridges	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	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”	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient use). Other package terms include pharmacy bulk package and imaging bulk package.	Not an injectable drug product	Acceptable

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Provides as follows: "*Do not put a blister card or strip back into the refrigerator after being opened or stored at room temperature*."	Acceptable
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	[redacted (b) (4)], blisters are stored at refrigerated condition, 2°C to 8°C (36°F to 46°F). [redacted (b) (4)] they are stored at room temperature at 20°C to 25°C (68°F to 77°F), excursions permitted 15°C to 30°C (59°F to 86°F). Once opened, they must be used within 3 days.	Acceptable
Include information about child-resistant packaging	N/A	Acceptable

1.2.6 Manufacturing Information After Section 17 (for drug products)

Items	Information Provided in the NDA	Assessor's Comments
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Tyvaso DPI manufactured by: MannKind Corporation Danbury, CT 06810 Tyvaso DPI manufactured for and distributed by: United Therapeutics Corp., Research Triangle Park, NC 27709	Acceptable

2.0 PATIENT LABELING

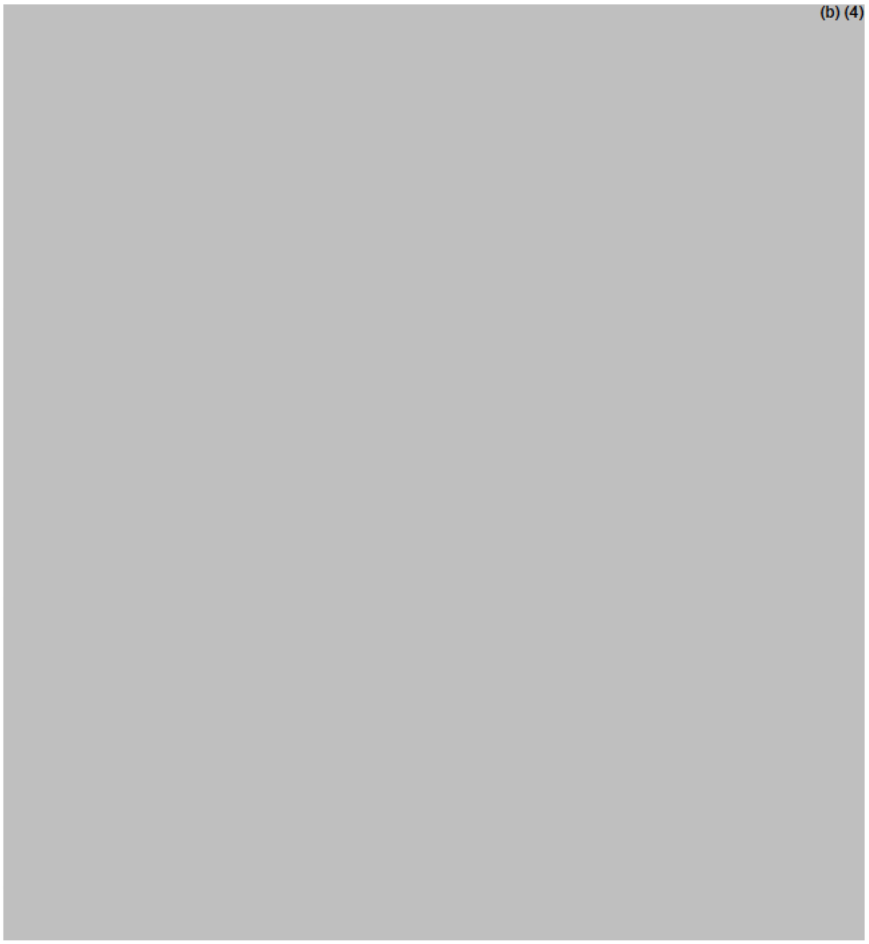
Assessment of Product Quality Related Aspects of Patient Labeling (e.g.,

Medication Guide, Patient Information, Instructions for Use): Acceptable.

Additional patient labeling/information has been provided. This includes step-by-step instruction for patient on how to open the cartridges from blister pack and how to insert into the inhalation device prior to use. This does not include any CMC specific information. This is more like a user guide for installing the drug loaded blister cartridge into the device. This will be further reviewed by the labeling reviewers.

3.0 CARTON AND CONTAINER LABELING

3.1 Blister Label



Blister labeling for other strengths are similar except for color code and strength.

Assessment on the container closure labeling:

Items	Information Provided in the NDA	Assessor's Comments
Proprietary name, established name, and dosage form (font size and prominence	TYVASO DPI™ (treprostinil) inhalation powder	Acceptable
Dosage strength	16 mcg, 32 mcg, 48 mcg, and 64 mcg	Acceptable
Route of administration	Oral inhalation	Acceptable
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not a salt	Acceptable
Net contents	16 mcg or 32 mcg or 48 mcg, or 64 mcg of treprostinil in each cartridge, (b) (4)	Acceptable
"Rx only" displayed on the principal display	yes	Acceptable
NDC number	yes	Acceptable
Lot number and expiration date	yes	Acceptable
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Unopened Blister Cards/Strips: Store refrigerated at 2°C to 8°C (36°F to 46°F). Discard unopened blister strips stored at room temperature after 5 weeks. Opened Blister Strips: Store at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to	Acceptable

	86°F) [See USP Controlled Room. Temperature]. INHALER STORAGE Store at 2°C to 25°C (36°F to 77°F) excursions permitted. May be stored refrigerated, but must be at room temperature before use.	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single patient-use)	Not an injectable product	Acceptable
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	Not applicable	Acceptable
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not Acceptable	Acceptable
Name of manufacturer/distributor	Tyvaso DPI manufactured by: MannKind Corporation Danbury, CT 06810 Tyvaso DPI (b) (4) distributed by: United Therapeutics Corp. Research Triangle Park, NC 27709	Acceptable
Medication Guide	Provided (Patient labeling)	Acceptable
No text on Ferrule and Cap Overseal	Not Applicable	Acceptable
When a drug product differs from the relevant USP	Not applicable	Acceptable

standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.		

Assessment of Carton and Container Labeling: *Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation: **Adequate**

Primary Drug Product Assessor Name and Date: Akm Khairuzzaman, Ph.D., 7/28/2021.
Secondary Assessor Name and Date (and Secondary Summary, as needed): Mohan Sapru, Ph.D., 7/28/2021.

Akm Khairuzzaman

Digitally signed by Akm Khairuzzaman
Date: 8/17/2021 08:04:00AM
GUID: 502d1ab500002aef5afaa6f74ddf7e69

Mohan Sapru

Digitally signed by Mohan Sapru
Date: 8/19/2021 01:53:20PM
GUID: 504f821600000ec6d20b59d2b68eb3d2