

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-387**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/10 See OMB Statement on Page 3.	
<b>PATENT INFORMATION SUBMITTED WITH THE FILING          OF AN NDA, AMENDMENT, OR SUPPLEMENT</b> <i>For Each Patent That Claims a Drug Substance          (Active Ingredient), Drug Product (Formulation and Composition)          and/or Method of Use</i>			
		NDA NUMBER 22387	
		NAME OF APPLICANT/NDA HOLDER United Therapeutics Corp	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) TYVASO (Proposed)			
ACTIVE INGREDIENT(S) treprostinil sodium		STRENGTH(S) 0.6 mg/ml	
DOSAGE FORM Inhalation Solution			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.			
<b>For hand-written or typewriter versions (only) of this report:</b> If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
<b>FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.</b>			
<b>For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.</b>			
<b>1. GENERAL</b>			
a. United States Patent Number 5,153,222		b. Issue Date of Patent Oct. 06, 1992	c. Expiration Date of Patent Oct. 16, 2014
d. Name of Patent Owner United Therapeutics Corporation		Address (of Patent Owner) 1735 Connecticut Avenue, N.W. Third Floor	
		City/State Washington, DC	
		ZIP Code 20009	FAX Number (if available) (202) 483-4005
		Telephone Number (202) 483-7000	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.) Not Applicable	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?			
		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?			
		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s) (as listed in the patent) 1 and 2 Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)  
 TYVASO is indicated for the treatment of pulmonary arterial hypertension in patients with NYHA Class III symptoms.  
 TYVASO is intended for oral inhalation use with an ultrasonic pulsated Optineb-ir nebulizer.

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

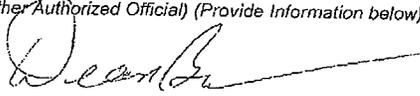
b(4)

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

13 June 2018

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Dean Bunce, Senior Vice President Regulatory Affairs and Compliance, United Therapeutics Corp	
Address One Park Drive, Suite 400	City/State Research Triangle Park, North Carolina
ZIP Code 27709	Telephone Number (919) 485-8350
FAX Number (if available) (919) 313-1298	E-Mail Address (if available) dbunce@unither.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

**PATENT INFORMATION SUBMITTED WITH THE FILING  
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and Composition)  
and/or Method of Use*

NDA NUMBER  
22387

NAME OF APPLICANT/NDA HOLDER  
United Therapeutics Corp

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)  
TYVASO (Proposed)

ACTIVE INGREDIENT(S)  
treprostinil sodium

STRENGTH(S)  
0.6 mg/ml

DOSAGE FORM  
Inhalation Solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number 6,756,033	b. Issue Date of Patent Jun. 29, 2004	c. Expiration Date of Patent Nov. 13, 2018
---	--	---

d. Name of Patent Owner United Therapeutics Corporation	Address (of Patent Owner) 1735 Connecticut Avenue, N.W. Third Floor	
	City/State Washington, DC	
	ZIP Code 20009	FAX Number (if available) (202) 483-4005
	Telephone Number (202) 483-7000	E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.) Not Applicable	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?  Yes  No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?  Yes  No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance (that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement)?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
1-3 and 5	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) TYVASO is indicated for the treatment of pulmonary arterial hypertension in patients with NYHA Class III symptoms. TYVASO is intended for oral inhalation use with an ultrasonic pulsated Optinex-ir nebulizer.
---	--

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

b(4)

**6. Declaration Certification**

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

*Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.*

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



13 June 2008

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Dean Bunce, Senior Vice President Regulatory Affairs and Compliance, United Therapeutics Corp	
Address One Park Drive, Suite 400	City/State Research Triangle Park, North Carolina
ZIP Code 27709	Telephone Number (919) 485-8350
FAX Number (if available) (919) 313-1298	E-Mail Address (if available) dbunce@unither.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/10 See OMB Statement on Page 3.	
<b>PATENT INFORMATION SUBMITTED WITH THE FILING          OF AN NDA, AMENDMENT, OR SUPPLEMENT</b> <i>For Each Patent That Claims a Drug Substance          (Active Ingredient), Drug Product (Formulation and Composition)          and/or Method of Use</i>			
		NDA NUMBER 22387	
		NAME OF APPLICANT/NDA HOLDER United Therapeutics Corp	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) TYVASO (Proposed)			
ACTIVE INGREDIENT(S) treprostinil sodium		STRENGTH(S) 0.6 mg/ml	
DOSAGE FORM Inhalation Solution			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
<b>1. GENERAL</b>			
a. United States Patent Number 6,765,117		b. Issue Date of Patent Jul. 20, 2004	c. Expiration Date of Patent Oct. 24, 2017
d. Name of Patent Owner United Therapeutics Corporation		Address (of Patent Owner) 1735 Connecticut Avenue, N.W Third Floor City/State Washington, DC	
		ZIP Code 20009	FAX Number (if available) (202) 483-4005
		Telephone Number (202) 483-7000	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.) Not Applicable City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

*Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:*

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s) (as listed in the patent)  Yes  No  
 Not applicable Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

*Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.*

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

*Dean Bunce*

Date Signed

*13 June 2008*

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Dean Bunce, Senior Vice President Regulatory Affairs and Compliance, United Therapeutics Corp	
Address One Park Drive, Suite 400	City/State Research Triangle Park, North Carolina
ZIP Code 27709	Telephone Number (919) 485-8350
FAX Number (if available) (919) 313-1298	E-Mail Address (if available) dbunce@unither.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/10 See OMB Statement on Page 3.	
<b>PATENT INFORMATION SUBMITTED WITH THE FILING          OF AN NDA, AMENDMENT, OR SUPPLEMENT</b>  <i>For Each Patent That Claims a Drug Substance          (Active Ingredient), Drug Product (Formulation and Composition)          and/or Method of Use</i>		NDA NUMBER 22387	
		NAME OF APPLICANT/NDA HOLDER United Therapeutics Corp	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) TYVASO (Proposed)			
ACTIVE INGREDIENT(S) tiropristinil sodium		STRENGTH(S) 0.6 mg/ml	
DOSAGE FORM Inhalation Solution			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
<b>For hand-written or typewriter versions (only) of this report:</b> If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
<b>FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.</b>			
<b>For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.</b>			
<b>1. GENERAL</b>			
a. United States Patent Number 6,521,212		b. Issue Date of Patent Feb. 18, 2003	c. Expiration Date of Patent Nov. 13, 2018
d. Name of Patent Owner United Therapeutics Corporation		Address (of Patent Owner) 1735 Connecticut Avenue, N.W. Third Floor	
		City/State Washington, DC	
		ZIP Code 20009	FAX Number (if available) (202) 483-4005
		Telephone Number (202) 483-7000	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1. e.) Not Applicable	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No			
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No			

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

**2. Drug Substance (Active Ingredient)**

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No
- 2.6 Does the patent claim only an intermediate?  Yes  No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No
- 3.2 Does the patent claim only an intermediate?  Yes  No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No
- 4.2 Patent Claim Number(s) (as listed in the patent)  Yes  No

6-12

Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)  
 TYVASO is indicated for the treatment of pulmonary arterial hypertension in patients with NYHA Class III symptoms.  
 TYVASO is intended for oral inhalation use with an ultrasonic pulsated nebulizer.

b(4)

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

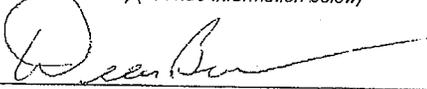
**6. Declaration Certification**

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

*Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.*

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



13 June 2008

**NOTE:** Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Dean Bunce, Senior Vice President Regulatory Affairs and Compliance, United Therapeutics Corp	
Address One Park Drive, Suite 400	City/State Research Triangle Park, North Carolina
ZIP Code 27709	Telephone Number (919) 485-8350
FAX Number (if available) (919) 313-1298	E-Mail Address (if available) dbunce@unither.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

## EXCLUSIVITY SUMMARY

NDA # 22-387

SUPPL #

HFD # 110

Trade Name TYVASO

Generic Name treprostinil solution for oral inhalation

Applicant Name United Therapeutics

Approval Date, If Known 7/30/09

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

### 1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-272

Remodulin (treprostinil) for IV/SC Injection

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

TRIUMPH I

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
IND # 70,362 YES  ! NO   
! Explain:

Investigation #2 !  
IND # YES  ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
!  
!  
YES  ! NO   
Explain: ! Explain:

Investigation #2  
!  
!  
YES  ! NO   
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

---

Name of person completing form: Dan Brum, Pharm.D.  
Title: RPM  
Date: 7/28/09

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.  
Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/  
-----

DANIEL BRUM

07/28/2009

Exclusivity Checklist/Summary unrelated to pediatrics

NORMAN L STOCKBRIDGE

07/28/2009

**PEDIATRIC PAGE**  
**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 22-387 Supplement Number: \_\_\_\_\_ NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: DCRP PDUFA Goal Date: 4/30/09 Stamp Date: 6/30/08

Proprietary Name: TYVASO

Established/Generic Name: treprostinil

Dosage Form: 0.6 mg/mL inhalation solution

Applicant/Sponsor: United Therapeutics

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) \_\_\_\_\_  
(2) \_\_\_\_\_  
(3) \_\_\_\_\_  
(4) \_\_\_\_\_

---

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): one  
(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** pulmonary arterial hypertension

**Q1:** Is this application in response to a PREA PMC/PMR? Yes  Continue  
No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMC/PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMC/PMR?

- Yes. Please proceed to Section D.  
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

\* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**  
 No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)  
 No: Please check all that apply:  
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)  
 Deferred for some or all pediatric subpopulations (Complete Sections C)  
 Completed for some or all pediatric subpopulations (Complete Sections D)  
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)  
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)  
(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): .....
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):  
 Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	___ wk. ___ mo.	___ wk. ___ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	___ yr. ___ mo.	___ yr. ___ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	___ yr. ___ mo.	___ yr. ___ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	___ yr. ___ mo.	___ yr. ___ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	___ yr. ___ mo.	___ yr. ___ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

# Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): .....

\* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

- Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):			Reason for Deferral			Applicant Certification †
			Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum				
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy):						

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	___ wk. ___ mo.	___ wk. ___ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	___ yr. ___ mo.	___ yr. ___ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	___ yr. ___ mo.	___ yr. ___ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	___ yr. ___ mo.	___ yr. ___ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	___ yr. ___ mo.	___ yr. ___ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	___ wk. ___ mo.	___ wk. ___ mo.
<input type="checkbox"/>	Other	___ yr. ___ mo.	___ yr. ___ mo.
<input type="checkbox"/>	Other	___ yr. ___ mo.	___ yr. ___ mo.
<input type="checkbox"/>	Other	___ yr. ___ mo.	___ yr. ___ mo.
<input type="checkbox"/>	Other	___ yr. ___ mo.	___ yr. ___ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cdcrpmhs@fda.hhs.gov](mailto:cdcrpmhs@fda.hhs.gov)) OR AT 301-796-0700.

existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	___ wk. ___ mo.	___ wk. ___ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	___ yr. ____ mo.	___ yr. ____ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

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

/s/

-----  
Dan Brum  
4/13/2009 03:10:09 PM

## Meeting Minutes

**Date:** May 22, 2009  
**Application:** NDA 22-387  
**Drug:** Tyvaso (treprostinil) Inhalation Solution  
**Sponsor:** United Therapeutics  
**Purpose:** To discuss outstanding issues related to the pending NDA  
**Meeting Type:** A

### FDA Attendees:

Norman Stockbridge, M.D., Ph.D.	Director, DCRP
Abraham Karkowsky, M.D., Ph.D.	Medical Team Leader
Mike Monteleone, M.S.	Regulatory Project Manager
Dan Brum, Pharm.D., RAC	Regulatory Project Manager
John Lawrence, Ph.D.	Statistician, Division of Biometrics I
Carol Holquist, R.Ph.	Director, DMEPA
Kellie Taylor, Pharm.D.	Team Leader, DMEPA
Judy Park, Pharm.D.	Safety Evaluator, DMEPA
Monica Cooper, Ph.D.	Chemist, ONDQA
Robert Kumi, Ph.D.	Clinical Pharmacologist, OCP

Note: CDRH Representatives—Ron Kaye, Sugato De, and Lester Schultheis were unable to attend the meeting.

### United Therapeutics and Consultants

Roger Jeffs	President
David Zaccardelli	Executive Vice President Pharmaceutical Development
Gene Sullivan	Chief Medical Officer
Dean Bunce	Executive VP, Regulatory Affairs and Compliance
Karl Gotzkowsky	Director, Product Development

**b(4)**

### Background:

NDA 22-387 for Tyvaso (treprostinil) inhalation solution was received on June 30, 2009 (PDUFA goal date July 30, 2009 due to the major amendment received April 9, 2009).

### *Purpose*

United Therapeutics requested this meeting to discuss issues related to their marketing application; what drug/device development information would the Agency require prior to approval; and what development work the Agency might allow the sponsor to perform post-approval (assumes approval).

Minutes preparation: *{See appended electronic signature page}*  
Dan Brum, Pharm.D., RAC

Concurrence, Chair: *{See appended electronic signature page}*  
Norman Stockbridge, M.D., Ph.D.

Drafted—5/26/09

Reviewed:

Park 5/27/09

Taylor 5/27/09

Cooper 5/29/09

Kumi 5/29/09

Karkowsky 6/1/09

Stockbridge 6/1/09

Finalized—6/1/09

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

/s/  
-----

Dan Brum  
6/1/2009 09:19:51 PM

Norman Stockbridge  
6/2/2009 09:01:00 AM



NDA 22-387

INFORMATION REQUEST LETTER

United Therapeutics Corporation  
Attention: Mr. Dean Bunce  
P.O. Box 14186  
55 TW Alexander Drive  
Research Triangle Park, NC 27709

Dear Mr. Bunce:

Please refer to your June 27, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tyvaso (treprostinil) Inhalation Solution.

We also refer to our letter dated March 3, 2009 and your submission dated March 25, 2009 (under IND 70,362). We have completed our review of your protocol entitled "Summative Usability Test of TYVASO Inhalation System" and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

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

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

1. Identification and prioritization of user tasks:

- The protocol does not include an analysis of use-risk (the most critical points in the process of use that if improperly done would result in either lack of effectiveness or diminished safety), meaningful results of a use-risk analysis, or list of use/interaction scenarios resulting from such an analysis upon which to structure your test. The concerns we previously mentioned should be considered in such an analysis but are not included in

any form in your protocol.

- Because potential use-risks have been neither identified nor prioritized, the protocol that you submitted does not identify and focus on high priority aspects of the use of the device-drug system, but rather takes an overly general non-specific approach to the use of the system.
- You plan to assess the potential for use errors, yet there are no specific examples or description of what these potential use errors are that the testing process or assessors will be prepared to record.

Please modify your protocol such that it includes a summary of what you perceive as the most important use errors on which the human factor/usability study will focus. Please list and describe specific use-errors that the testing will be designed to evaluate and justify that your list is reasonably comprehensive.

## 2. Evaluate essential components of user interaction

- The “simulated use” as described in your protocol does not include breathing through the device. Instead, the user is instructed to “simulate inhaling one cycle of breaths” and to “tell the administrator when you would inhale or exhale”. We agree that no dosing should occur during the HF study. It is, however, essential that all critical aspects of the interaction between the user and the device that interact with the breath counter and other components be evaluated, and this cannot be done adequately if the user does not actually simulate use by inhaling through the device.

Please modify your protocol to include simulated use that decomposes successful dosing interaction into critical components that can be observed and assessed by a trained observer. The input of clinical expertise regarding specific requirements of user performance will be necessary and your assessors will need to be trained accordingly to enable them to assess essential behaviors. The expert identification of critical factors should be discussed in your protocol as part of the task analysis and prioritization previously discussed.

In order to assess the reliability of the entire process, a pharmacokinetic analysis of drug concentrations will be needed to assess the contribution of human factors problems on the variability in exposure ( $C_{max}$ ).

## 3. Training

The protocol needs further clarification on the nature and extent of the training that will be given to test participants and how the training, the lag time between training and testing, and the testing itself will reasonably represent realistic conditions. The Training Sessions, Notes section indicates the intent to consider patients “potential outliers” if they do not pass the patient competency assessment during training. To exclude patients who are not high functioning individuals appears to be an attempt to select only high performing people for the study group, and this exclusion therefore is inconsistent with the concept of sampling from a population of “intended users.”

#### 4. Screening participants

- The protocol indicates that participants will not be included unless they are either native English speakers or “highly proficient” with respect to reading and speaking. This appears to be unrealistic and not representative of home users of medical devices.

Please modify the recruiting screening such that it does not systematically exclude representative members of the intended user population. However, we do recommend that you do exclude participants who are experienced in the use of nebulizers.

#### 5. Testing procedure

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

Please modify your protocol such that evaluation will be made on users interacting with the device in a more realistic fashion. Rather than repeated interruptions with questions, users should be allowed to proceed with uninterrupted use of the device while being assessed. More emphasis should be placed on assessment of performance during use of the device, and any questioning should be held until after the use session is concluded.

#### 6. Data reduction, analysis, and reporting

- The protocol is not specific with respect to how test data will be tabulated or analyzed.
- The current description of how data will be reported is vague.

The portion of the protocol that describes the test report should address all types of data you plan to collect and how those data will be handled and reported.

#### 7. Measures of user performance and acceptable performance criteria (Pass/Fail criteria)

- We did not see meaningful criteria for the measurement of user performance included in your draft protocol.
- The data elements that are listed on page 6 of your draft protocol are not adequately defined or described. For instance, the current protocol states that “Observed use errors” will be sought, but there is no explanation of what these might be or why they are important. Similarly, the nature and relevance of “Task times (stopwatch accuracy)”, participant ratings of “ease of use”, and responses to interview questions are also unclear. You state that testing will be videotaped and that participants will be photographed but you do not explain how videotapes or photographs will be analyzed.

Meaningful measures of performance provide a basis for reasonable assessment of the use of a device. You should be testing for the presence of patterns of use error that could compromise safety and effectiveness for this device in a population meant to use this system.

#### 8. Modifications to device design

The protocol describes a “summative” test which equates to a “validation” of use. If testing results indicate problematic performance with the device and you address this with some form of mitigation (to include design modification), the resulting modified device may need further validation.

As discussed during our teleconference on March 30, 2009, we are willing to discuss any of these issues further if additional clarification is needed.

If you have any questions, please call Dan Brum, PharmD, RAC, Regulatory Project Manager, at 301-796-0578.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal Products  
Office of New Drugs  
Center for Drug Evaluation and Research

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

/s/

-----  
Norman Stockbridge  
4/6/2009 11:32:51 AM



NDA 22-387

INFORMATION REQUEST LETTER

United Therapeutics Corporation  
Attention: Mr. Dean Bunce  
P.O. Box 14186  
55 TW Alexander Drive  
Research Triangle Park, NC 27709

Dear Mr. Bunce:

Please refer to your June 27, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tyvaso (treprostinil) Inhalation Solution.

We are reviewing the NDA and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

**Device – Human Factors**

The Agency is concerned that the current design of the device and the materials supporting its use (e.g., user manual) could possibly induce or allow use-errors that could compromise the user's ability to deliver medication properly and thereby pose certain risks to the patient. Please indicate what Human Factors studies your device has undergone to identify any risks and potential consequences associated with user error, and validate the instructions. Please provide the protocols, criteria for assessing whether the instructions were vulnerable to error (pass/fail criteria), results, conclusions, and subsequent modifications to the instructions or to the device.

The Agency expects you to perform your own comprehensive analysis of use-related risk, including the following:

- Whether users can properly dose themselves with a total of nine breaths using the currently designed breath counter mechanism. This counter counts only up to three and the patient must restart the program two additional times to receive the required nine breaths.
  - The difficulty in viewing the counter in its current position relative to the user's eyes during the use of the device.
  - The ability of the user to remember where in the sequence three groups of three breaths was just completed.
  - The requirement for the user to switch the device on/off after each group of three breaths.

- Possible risk to the user should the dose be less than the prescribed dose, given the apparently challenging requirement for the user to take nine deep breaths within the specified time limit of ninety seconds.
- Whether inhalation or exhalation into the mouthpiece triggers a change in the count displayed by the breath-counter mechanism, whether this trigger is time-related, and whether the user needs to be aware of how this process operates to ensure proper use and delivered dosage.
- The ability of users to assemble your device correctly under realistic conditions consistent with home-use to include proper physical connection of device components and loading of appropriate levels of medication into the medicine cup.
- Whether the two included filters are interchangeable without impacting proper performance of your device, or if not, whether there is risk of users inadvertently reversing their location on subsequent assemblies and uses.
- The extent to which proper cleaning and maintenance is required for proper device operation, and the extent to which the user materials convey this need and the process for performing these maintenance activities in a home environment.
- The extent to which there is a risk of contamination of the medicine and the contact fluid while dropping the medicine cup into the contact fluid chamber. The medicine can be contaminated by hand or it can spill over the medicine cup into the contact fluid during this process.
- The extent of device failure or problems if non-distilled water is used as the contact fluid (e.g., tap water).

For more information regarding Human Factors, please visit <http://www.fda.gov/cdrh/humanfactors/>.

#### **Drug and Device – Patient/User Labeling**

With regard to labeling for the OPTINEB-ir- [redacted] device, you submitted a “user manual”. We have reviewed the user manual and believe it would be too difficult for patients and users of the device to comprehend. Additionally, the manual in its present form does not include any information about the drug, e.g., indications for use, side effects, etc. **b(4)**

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

We are providing you with a couple of suggestions to consider as you revise your documents: IFUs: The following sections with diagrams should be considered for inclusion:

- “preparing for your treatment”,
- “using your OPTINEB-ir- [redacted]”, **b(4)**
- “maintenance and cleaning”, etc.

Each diagram should be clearly labeled with references in the text that correspond to each diagram.

PPI: Information regarding indications and usage, contraindications, and other drug-specific information are frequently included in PPIs. You may refer to 21 CFR Section 208 for a list of subheadings to consider as you develop a PPI.

The general recommendations listed below are consistent with current research to improve risk communication to a broad audience, including those with lower literacy. Please consider these recommendations as you prepare the requested labeling revisions:

The Flesch Reading Ease and Flesch Kinkaid Grade Level scores in the DRAFT OPTINEB-ir- User Manual are 49.5% and 9.5, respectively. 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% (60% corresponds to an 8<sup>th</sup> grade reading level). Please ensure the materials you submit for review meet these criteria. b(4)

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We recommend that you reformat the Patient Package Insert and Instructions for Use using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

### **Label, Labeling and Packaging Configuration**

#### ***Packaging Configuration:***

We note that the inhalation solution will be packaged in four unmarked low density polyethylene (LDPE) ampules in a single foil wrap. This configuration is a concern since the four unmarked LDPE ampules may be separated from the pouch after opening. Drug products packaged in LDPE plastic ampules may be more easily confused with one another since few have distinguishing characteristics traditionally utilized on medication containers such as paper labels, color, etc. Multiple ampules in a single foil wrap lend themselves to removal or tearing also affecting the legibility of the foil overwrap itself. We have learned through post-marketing reports that the embossed/debossed lettering is difficult to read, if not poorly legible once removed from the foil overwrap. We ask you to consider foil-overwrapping each individual low-density polyethylene (LDPE) ampule to help maintain the legibility of the product name and strength.

#### ***Carton Labeling:***

Some key information (e.g., route of administration, net quantity) is not prominently displayed on the principal display panel. We suggest that you increase the prominence of this information. Consider relocating the established name beneath the proprietary name. Additionally, consider relocating the "contents" information so that the proprietary name, established name, and the dosage form can be separated from the rest of the labeling information and readily recognized.

NDA 22-387 treprostinil inhalation solution

We have completed our review of the proposed proprietary name, Tyvaso, and have concluded that it is acceptable. However, if **any** of the proposed product characteristics are altered prior to approval of the marketing application or the approval of the NDA is delayed beyond 90 days of this letter, this finding is rescinded and the proprietary name should be resubmitted for review.

We encourage you to request a teleconference to further discuss any of these issues.

If you have any questions, please call Dan Brum, PharmD, RAC, Regulatory Project Manager, at 301-796-0578.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal Products  
Office of New Drugs  
Center for Drug Evaluation and Research

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

/s/

-----  
Norman Stockbridge  
3/3/2009 01:56:36 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-387

INFORMATION REQUEST LETTER

United Therapeutics Corporation  
Attention: Dean Bunce, Sr. Vice President, Regulatory Affairs  
One Park Drive, Suite 400  
P.O. Box 14186  
Research Triangle Park, NC 27709

Dear Mr. Bunce:

Please refer to your June 27, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tyvaso (treprostinil) Inhalation Solution.

We also refer to your submissions dated July 3, 2008 and October 29, 2008.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Your alternate HPLC method \_\_\_\_\_ for assay and impurities was not fully validated. The following validation parameters were missing: intermediate precision, robustness, system suitability, response factor determination, and stability-indicating determination. In addition, the method was not validated with respect to the known impurities, \_\_\_\_\_. Provide the full validation information for this method. b(4)
2. Your drug product specification limit of \_\_\_\_\_ for total related substances is not justified based on release and stability data showing total impurity levels of \_\_\_\_\_. A limit based on mean plus three standard deviations would be more appropriate. Tighten your acceptance criterion for total related substances and provide a justification for the new limit. b(4)
3. Provide drawings and specifications for the primary packaging components (LDPE vials and laminate foil).
4. Provide a DMF reference and a Letter of Authorization for the laminate foil.
5. Provide an in-use stability study for the drug product when stored in the nebulizer. The study submitted previously under IND 70,362 did not adequately replicate the worst-case conditions used in the clinic, as only 3 breaths/pulses were used in each of 4 sessions over 24 hours. The in-use study should monitor the stability of the product using a total of 12 breaths for each of 4 sessions per day. It is recommended that the stability study cover at least 72 hours for added assurance of the stability of the product. In addition, it is recommended that the nebulizers (containing the drug product) be stored under normal lighting conditions during testing, not in dark chambers.

6. Your response to Review Issue #2 in the 74-Day Letter is not acceptable. The established name for the drug product should be 'treprostini!' and not 'treprostini! sodium' to match the dosage form strength to the established name. The current USAN name, adopted/published in the USP dictionary in 2002, is 'treprostini!.' You may also consider revising the established name for Remodulin Injection to 'treprostini!' for consistency.

If you have any questions, call Don Henry, Regulatory Project Manager, at 301-796-4227.

Sincerely,

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief I  
Division of Pre-Marketing Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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

/s/

-----  
Ramesh Sood  
1/13/2009 03:57:17 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

**INFORMATION REQUEST LETTER**

NDA 22-387

United Therapeutics Corp  
Attention: Mr. Dean Bunce  
One Park Drive  
Suite 400  
Research Triangle Park, North Carolina 27709

Dear Mr. Bunce:

Please refer to your new drug application (NDA) dated June 27, 2008, received June 30, 2008, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for treprostinil inhalation solution, 0.6 mg/mL.

We are reviewing the sterility portion of your application and request that you provide the following information or reference the specific location in your NDA:

- A narrative describing the environmental microbiological monitoring program which includes information regarding the sampling and testing methods, incubation conditions, alert and action limits, and routine production monitoring frequency.
- Data sets supporting the holding periods listed in Module 3.2.P.3.5 of the NDA.
- A narrative describing the media fill process simulation procedures, acceptance criteria, and actions to be taken following a failed media fill. Include the frequency at which process simulations are performed, and data sets in support of the manufacture of the subject drug product at the Catalent Pharma Solutions manufacturing facility.

If you have any questions, please call Dan Brum, Pharm.D., Regulatory Health Project Manager, at (301) 796-0578.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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

/s/

-----  
Norman Stockbridge  
11/20/2008 06:35:57 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-387

United Therapeutics Corp  
Attention: Mr. Dean Bunce  
One Park Drive  
Suite 400  
Research Triangle Park, North Carolina 27709

Dear Mr. Bunce:

Please refer to your new drug application (NDA) dated June 27, 2008, received June 30, 2008, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for treprostinil inhalation solution, 0.6 mg/mL.

We also refer to your submissions dated July 3, August 14, and August 26, 2008.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is April 30, 2009.

During our filing review of your application, we identified the following potential review issues:

1. Container-closure integrity and bacterial filter retention data summaries are not provided. Once these studies are complete in September 2008 as indicated, please submit the reports.
2. The established name should be 'treprostinil' and not 'treprostinil sodium' to match the dosage form strength. Please update all labels accordingly. Note: The chemical name, molecular formula, molecular weight, and structural formula within the Package Insert's Description section should be revised.
3. In section 3.2.S.4.4 *Batch Analyses*, the first page of the certificate of analysis (COA) for drug substance lot DB06005 was omitted. Please provide the missing information.
4. Please provide representative COAs for each of the excipients used in the drug product.
5. Please provide a list of acceptance testing performed by the drug product manufacturer on incoming batches of each excipient and the drug substance.
6. Sections 3.2.P.4.5 and 3.2.P.4.6 were omitted. Please provide the missing information.

7. Please include the Weight Loss test and propose an acceptance criterion in your drug product specification table with a footnote that this parameter is tested only on stability. Update your post-approval stability protocol to include this test.
8. Since stability data from only two full-scale batches were included in the submission, your post-approval stability commitment should include both long-term and accelerated conditions for the first marketed batch.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, please call Dan Brum, Pharm.D., Regulatory Project Manager, at (301)796-0578.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal  
Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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

/s/

-----  
Norman Stockbridge  
9/3/2008 06:32:41 AM

## Meeting Minutes

**Date:** May 16, 2008  
**Application:** IND 70,362  
**Drug:** treprostinil inhaled  
**Sponsor:** United Therapeutics  
**Purpose:** Pre-NDA Meeting  
**Meeting Type:** B

### FDA Attendees:

Norman Stockbridge, M.D., Ph.D.	Director, DCRP
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical Officer
Robert Kumi, Ph.D.	Clinical Pharmacologist
Kasturi Srinivasachar, Ph.D.	Pharmaceutical Assessment Lead, ONDQA
Monica Cooper, Ph.D.	Quality Reviewer, ONDQA
Xavier Joseph, DVM	Pharmacologist
Michael Husband, M.S.	Biomedical Engineer, CDRH
Edward Fromm, R.Ph.	Chief, Regulatory Health Project Manager
Dan Brum, Pharm.D., MBA	Regulatory Project Manager, DCRP

### Representing UT

Dean Bunce	Senior Vice President, Regulatory Affairs
Mary A. Matthew	Director, Regulatory Affairs
Karl Gotzkowsky	Director, Product Development
Carl Arneson	Director, Biostatistics and Data Management
David Zaccardelli	Executive Vice President, Pharmaceutical Development
Hilary Hafeken	Regulatory Document Manager
Rex Mauthe	Director, Regulatory Affairs
Eugene Sullivan	Chief Medical Officer
James Levin	Chief Manufacturing Officer
Roger Jeffs	President

### Other Participants:

b(4)



2. United Therapeutics will be proposing the following indication in the NDA, as noted in the attached draft package insert:

“Treprostinil for Inhalation, 0.6 mg/mL is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III — severity of disease. In a controlled trial, Treprostinil for Inhalation improved exercise capacity in patients concurrently receiving either a phosphodiesterase-5 (PDE-5) inhibitor or an endothelin receptor antagonist (ERA) for treatment of pulmonary arterial hypertension”.

b(4)

*Does the Division agree that the above listed studies, supported by NDA 21-272, are adequate to support submission of an NDA?*

**FDA Response:** This is a review-related issue that cannot be answered at this time. We note, however, that you have minimal dose data and minimal data that the effect persists more than the duration of the study. Those deficiencies seem less acceptable than they did when there were few therapeutic alternatives.

**Discussion during the meeting:** The sponsor explained that the effect on six minute walk distance is similar between the 6 and 12 week time points. The Division said that a short-term, parallel-design, fixed-dose study with only a modest dose range is only marginally useful in understanding the appropriate usable dose range, particularly as the disease process progresses.

The Division said there are two issues to consider with regard to persistence of effect: 1) Demonstrating an effect during the interdosing interval and 2) Demonstrating an effect after a longer period of treatment (e.g., one year) via a placebo-controlled withdrawal study design. The sponsor is concerned that providers may be reluctant to enroll patients in a placebo-controlled withdrawal study. Other symptomatic benefits (not outcome benefits) can be tested by this design.

3. United Therapeutics will present data from *LRX-TRIUMPH 001: Double Blind Placebo Controlled Clinical Investigation into the Efficacy and Tolerability of Inhaled Treprostinil Sodium in Patients with Severe Pulmonary Arterial Hypertension (TRIUMPH I STUDY)* as detailed in the attached Statistical Analysis Plan, submitted to IND 70,362 on 27 September 2007 (Serial No. 0067) and amended 26 October 2007 (Serial No. 0072).

United Therapeutics will be submitting two study reports for this study. The first study report will include all data for the 12 week, placebo-controlled part of the study. The second study report will include data for the long-term, open-label part of the study with a cut-off date of 1 January 2008.

*Does the Division accept this approach for LRX-Triumph 001 study reports?*

**FDA Response: Yes.**

**There was no further discussion during the meeting.**

4. As stated in the 1 November 2006 meeting minutes (attached), the Division requested that all studies from NDA 21-272 be included in the NDA for treprostinil for inhalation. United Therapeutics will submit all clinical and nonclinical study reports submitted in NDA 21-272, as legacy study reports, in accordance with *Guidance for Industry Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* and as noted in the attached Module table of contents. We also would like to request that the case report forms and data tabulations from these legacy reports not be included in this submission, but be available on request.

*Is this approach acceptable to the Division?*

**FDA Response: Yes.**

**There was no further discussion during the meeting.**

5. United Therapeutics proposes that Integrated Summaries of Safety (ISS) and Efficacy (ISE) for subcutaneous and intravenous Remodulin from NDA 21-272 be included as Appendices to the treprostinil for inhalation ISS and ISE. We also propose that all other summaries submitted in NDA 21-272, be included as appendices to the inhaled summaries, instead of being integrated into the summaries for treprostinil for inhalation.

*Is this approach acceptable to the Division?*

**FDA Response: Yes.**

**There was no further discussion during the meeting.**

*Quality*

6. The NDA for Inhaled Remodulin will include a previously approved drug substance (treprostinil sodium in accordance with NDA 21-272), a drug product (same formulation as Remodulin in NDA 21-272 except without \_\_\_\_\_ ) and a nebulizer device for delivery of the drug product to the patient. The sponsor intends to include the required information pertaining to the device within the CMC section (Module 3) of the NDA as shown in the attached Table of Contents.

b(4)

*Does the agency accept this approach for this NDA?*

**FDA Response: Yes, please see response to question #1.**

**Please see "Discussion during the meeting" under question #1.**

7. The sponsor performs the following assays to release Drug Product (DP) for Treprostinil for Inhalation, 0.6 mg/mL (treprostinil sodium drug substance manufacturing and release are as approved in NDA 21-272). Treprostinil for Inhalation, 0.6 mg/mL is manufactured by Catalent Pharma Solutions in a 2.9 mL LPDE ampoule, and will be packaged in groups of 4 ampoules.

*Does the agency agree that this quality control program for release testing of drug product is acceptable?*

**FDA Response: We have the following comments and requests –**

- **In addition to the drug substance specifications approved in NDA 21-272, you have been monitoring residual methanol and microbial limits in this IND. Please provide justification for why those tests are no longer needed for the NDA.**
- **In the drug product specifications, you should specify upper and lower limits for osmolality.**
- **Within the NDA, we ask that you provide a comprehensive regulatory specification table that includes all the testing (with acceptance criteria) that will be performed on the drug product, both at release and during the stability studies.**

**Discussion during the meeting: The sponsor agreed with each of the above points. It was clarified that residual methanol and microbial limits are currently being tested for the drug substance used in Remodulin and these tests will be continued for treprostinil for inhalation.**

8. The sponsor intends to perform Drug Product stability in accordance with the following stability testing and plans (Drug Substance stability will be performed in accordance with the testing program already approved in NDA 21-272).

*Does the agency agree that these plans are adequate to support an acceptable NDA submission?*

**FDA Response:** We have the following comments and requests --

- Please follow the recommendations in the FDA guidance entitled, "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation" (July 2002). According to this guidance, the drug product should be evaluated for compounds that leach from elastomeric or plastic components of the container closure system (and any inks, paper, or adhesive components from the labels or packaging) during your stability studies. If a correlation is established between the levels of leachables in the drug product (through the shelf life or until an equilibrium is demonstrated) and the extractables of a drug product container and closure components, evaluation of leachables in future routine stability studies may not be needed.
- You should propose limits for weight loss.
- Please clarify that these stability studies are performed on the unprotected product (without foil overwrap).
- You should also perform photostability studies on the unprotected product (without foil overwrap).

**Discussion during the meeting**

- **Leachables and extractables:** The sponsor will include detailed information and literature references \_\_\_\_\_ in their NDA. b(4)
  - **Weight loss:** An upper limit for weight loss will be proposed in the NDA.
  - **Overwrap:** The sponsor agreed that the labeling and packaging should state that ampoules must remain in the foil overwrap until just prior to use.
  - **Stability:** The sponsor will clarify where the study was done with the unprotected ampoules and whether light was used in the study.
  - **Photostability:** The sponsor will report all data in the NDA.
9. United Therapeutics intends to submit the NDA to include the current nebulizer device (Opti-neb) which is provided by a contract vendor and has been used in the clinical trials to date. b(4)

b(4)

10. Labeling requirements for the nebulizer – United Therapeutics proposes the following labeling for the nebulizer:

*Does the agency agree that this is acceptable?*

b(4)

**FDA Response: Yes, assuming the full product labeling and instructions for use are unchanged from those cleared in the 510(k).**

**Discussion during the meeting: Please see the response and discussion related to question #9.**

11. Leachables/Extractables testing: For extractables testing United Therapeutics plans to investigate all of the plastic pieces and the O-ring in the ventilatory gas pathway in contact with the drug product; these include the medicine cup, dome assembly, inhalation/exhalation piece, and the mouthpiece on the Nebu-Tec device. The extractable testing will consist of a \_\_\_\_\_ extraction method and analysis by GC, LC, and ICP. If any compounds of interest are identified in the extractables testing, they will be further evaluated in a leachables study.

b(4)

*Does the agency agree that this is acceptable?*

**FDA Response: Yes.** \_\_\_\_\_

b(4)

\_\_\_\_\_. Please provide a toxicological evaluation of any extractables found and submit the results of USP Biological Reactivity Tests (USP <87> and <88>).

**Discussion during the meeting:** The sponsor plans to provide information on extractables testing and a toxicological evaluation.

The sponsor does not believe that USP <87> and <88> are applicable in this situation since there is no heat applied to the device and the drug supply and output is at room temperature. The sponsor also mentioned that the pulses are short, the total time of use is limited, and there is a water bath to absorb any potential heat generated by the device. The Division believes that USP <87> and <88> apply to all devices, not just those used at higher temperatures. These tests determine whether there is any biological reactivity to any plastic or elastomeric component in the device. Thus, we recommend this testing be performed.

12. Biocompatibility testing: For biocompatibility testing United Therapeutics plans to investigate all of the plastic pieces and the O-ring in the ventilatory gas pathway in contact with the drug product; these include the medicine cup, dome assembly, inhalation/exhalation piece, and the mouthpiece on the Nebu-Tec device. We are treating these devices as tissue/bone/dentin communicating, with chronic exposure (> 30 days) and are testing for cytotoxicity, sensitization, and intracutaneous reactivity per ISO-10993.

*Does the agency agree that this is acceptable?*

**FDA Response: Yes.**

**Discussion during the meeting:** The device components within the gas path can be considered as external communicating devices, tissue communicating, and of permanent duration for purposes of testing, since the device is a conduit to the lung, and the device is to be use chronically. FDA General Program Memorandum #G95-1 suggests use of ISO 10993-1 for initial biocompatibility test for consideration: these include cytotoxicity, sensitization, genotoxicity, and implantation.

### **Additional Comments**

**Pharmacology:** You note that your 2-year inhalation carcinogenicity study in rats [which has not yet begun] will be ongoing at the time of NDA submission in June 2008. Because of the Division's previous acknowledgment that there is a possibility that, depending on the outcome of your clinical trial, a completed carcinogenicity study may not be required to support approval of your product, the absence of carcinogenicity study data will not be considered a filing issue.

**Discussion during the meeting:** The sponsor plans to follow the Executive CAC's advice to repeat the range-finding study prior to initiating a two-year rat study. The sponsor said that the two-year rat study, therefore, will not be initiated by the time the NDA is submitted (e.g., June 30, 2008).

**Clinical Pharmacology:** Please include the following in your NDA:

1. Electronic datasets for all relevant pharmacokinetic studies.
2. Tabular summary of all bioanalytical methods, indicating method, study, formulation and assay validation information (sensitivity, linear range, coefficient of correlation and measures of accuracy and precision).
3. Clinical pharmacology summary that follows the QBR (Question Based Review) format. We will provide you a template of the QBR format in a subsequent communication.

**There was no further discussion during the meeting.**

**Administrative:** Please note that Dan Brum sent Dean Bunce an email on May 6, 2008 requesting that Ann Graham not participate in the May 16, 2008 Pre-NDA discussion. The sponsor agreed to this request in an email dated May 7, 2008.

### **Additional Post-Meeting Comments:**

In slide #8, the sponsor asked the Division, "May the drug substance be referenced to NDA 21-272 and not repeated in the inhaled NDA?" The Division responded yes, this is acceptable. However, please include a copy of the drug substance specifications and COAs (certificates of analysis) for the drug substance batches used to manufacture the drug product registration batches in the NDA submission.

Signature, Chair: *{See appended electronic signature page}*  
Norman Stockbridge, M.D., Ph.D.

Brum 5/19/08  
Cooper 5/19/08  
Srinivasachar 5/19 /08  
Joseph 5/20/08  
Kumi 5/20/08  
Husband 5/21/08  
Karkowksy 5/22/08  
Fromm 5/22/08  
Stockbridge 5/23/08

cc: Sponsor's slide presentation enclosed

Linked Applications

Sponsor Name

Drug Name

IND 70362

UNITED THERAPEUTICS  
CORP TREPROSTINIL SODIUM (INHALATION)

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

/s/

DANIEL BRUM  
05/24/2008

NORMAN L STOCKBRIDGE  
05/27/2008



U.S. PATENT OFFICE  
Washington, D.C. 20503  
Patent and Trademark Office, No. 877071  
U.S. PATENT OFFICE  
Washington, D.C. 20503

26 June 2008

Norman Stockbridge, M.D., Ph.D., Director  
Division of Cardiovascular and Renal Products (HFD-110)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Central Document Room  
5901B Ammendale Road  
Beltsville, Maryland 20705

RE: **NDA 022387**  
**Tyvaso™ (treprostinil sodium) Inhalation Solution**  
**Sequence No: 0000**

**INITIAL APPLICATION**

Dear Dr. Stockbridge:

Pursuant to 21 CFR §314.50, United Therapeutics Corporation hereby submits the initial New Drug Application for Tyvaso (treprostinil sodium) inhalation solution, in eCTD format for review by the Division of Cardiovascular and Renal Products. Tyvaso is our proposed trade name.

Tyvaso (treprostinil sodium) inhalation solution is submitted for the indication of Pulmonary Arterial Hypertension (PAH). United Therapeutics was granted Orphan designation for the indication Pulmonary Arterial Hypertension November 2, 1999. A copy of the letter is attached.

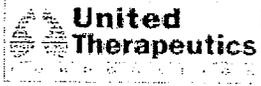
As agreed at the 16 May 2008 pre-NDA meeting, sections 3.2.S and 2.3.S, sections for the active pharmaceutical ingredient (API), treprostinil, are included by reference to approved NDA 21-272. However, as requested, the API specifications and and COAs (certificates of analysis) for the API used to manufacture the drug product registration batches are included in 3.2.S.4.

In accordance with 21 CFR §314.55(d), we hereby request an exemption for pediatric use information for Tyvaso.

Pursuant to 21 CFR §314.108(b)(2), we hereby request a three-year period of exclusivity for Tyvaso.

By this letter United Therapeutics Corporation hereby certifies that we did not and will not use in any capacity the services of any person debarred as defined in the Food, Drug and Cosmetic Act, Section 306.

UNITED THERAPEUTICS CORPORATION



This submission has been scanned for viruses using Trend Micro Clinet/Server Security Agent and is virus free. The approximate size of the submission is 3.0 GB.

Should you have any questions concerning the contents of this application, please do not hesitate to contact me at 919-485-8350, extension 1218 or by email at [dbunce@unither.com](mailto:dbunce@unither.com). For any technical inquiries, please contact Hilary Hafeken at 919-485-8350, x1219 or by email at [hhafeken@unither.com](mailto:hhafeken@unither.com). Both can be reached by facsimile at 919-313-1298.

Respectfully,

*{See Appended Electronic Signature Page}*

Dean Bunce  
Senior Vice President Regulatory Affairs and Compliance

<u>Approver Name</u>	<u>Approval Function</u>	<u>Approval Type</u>	<u>Date/Time</u>
Dean Bunce	Regulatory	Approve	2008/06/26 15:33:00

**DIVISION OF CARDIOVASCULAR & RENAL PRODUCTS  
FOOD AND DRUG ADMINISTRATION**



**US Mail address:**  
CDER, DCRDP (HFD-110)  
10903 New Hampshire Ave.,  
Silver Spring, MD 20993-0002

FDA  
10903 New Hampshire Ave  
Silver Spring, MD 20993-00025600

**This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCRDP (HFD-110); 10903 New Hampshire Ave., Silver Spring, MD 20993-0002**

**Transmitted via email:** glebovic@lungrx.com

**Attention:** Gabriel Lebovic

**Company Name:** Lung Rx, Inc.

**Phone:** 240-281-3203

**Subject:** IND 70,362 1 Nov 06 Meeting Minutes

**Date:**

**Pages including this sheet:**

**From:** CDR John David

**Phone:** 301-796-1059

**Fax:** 301-796-9838

**\*\*\*\*\*PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

FDA Division of Cardiovascular and Renal Products Meeting Minutes

Sponsor: Lung Rx, Inc.  
Drug: Treprostinil Sodium for Inhalation  
IND: 70,362  
Date of request: August 7, 2006  
Date request received: August 10, 2006  
Date of confirmation: August 18, 2006  
Date of pre-meeting: October 18, 2006  
Date preliminary responses sent: October 25, 2006  
Date of receipt of Sponsor Responses: October 30, 2006  
Date of meeting: November 1, 2006 (sponsor requested)  
Time: 10-11:30 am  
Place: 10903 New Hampshire Ave.  
Bldg #22, Room 1311  
Silver Spring, MD 20993

Type/Classification: Type C/Guidance

Meeting Chair: Norman Stockbridge, M.D., Ph.D.

Meeting recorder: John David

FDA Participants:

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products, HFD-110
Abraham Karkowsky, M.D.	Team Leader, Medical Officer, HFD-110
Valerie Freidlin, Ph.D.	Statistician, HFD-710
Robert Kumi, Ph.D.	Clinical Pharmacology, HFD-860
Charles Resnick, Ph.D.	Team Leader, Pharmacology, HFD-110
Xavier Joseph, Ph.D.	Pharmacologist, HFD-110
Kasturi Srinivasachar, Ph.D.	Chemistry Pharmaceutical Assessment Lead, ONDQA
Ann Graham	Acting Branch Chief, HFZ-480
Michael Husband	Medical Devices Consultant, HFZ-480
John David	Regulatory Health Project Manager, HFD-110

Lung Rx, Inc. Participants:

Dr. Robert Roscigno, Ph.D.	President and COO
Dr. Eugene Sullivan, M.D.	Chief Medical Officer
Mr. Ted Staub, M.S.	Senior Director of Clinical Development
Mr. Gabriel Lebovic, M.S.	Director of Regulatory Affairs
Dr. Fiona Mortimer, Ph.D.	Manager of European Regulatory Affairs

b(4)

**Background:**

Lung Rx, Inc. plans to file the safety and efficacy data for Treprostinil Sodium for Inhalation as an NDA marketing application and to cross-reference the preclinical, clinical and CMC data to NDA 21-272, for the subcutaneous and intravenous Remodulin<sup>®</sup>, which contains the very same active drug substance.

Lung Rx, Inc. believes that the discussions, comments and agreements from this Type B Guidance Meeting are crucial for the expeditious completion of the drug development program of Treprostinil Sodium for Inhalation, 0.6 mg/mL, which may be indicated for the treatment of pulmonary arterial hypertension. They are seeking advice on a wide range of the preclinical, clinical, statistical and CMC issues, which are considered highly relevant to the potential filing of the marketing application. Also, they wish to discuss with the Division clinical and statistical recommendations, which were described in the June 8, 2006 letter to Lung Rx, Inc., their plan for the potential filing of a rolling NDA submission and whether the Division prefers that all relevant preclinical, clinical and CMC data from NDA 21-272 for Remodulin<sup>®</sup> IV and Remodulin<sup>®</sup> SC (United Therapeutics, Inc.) be included in the electronic NDA in the CTD format or that such information should only be cross-referenced.

The delivery method of product is by NEBU-TEC's OPTINEB<sup>®</sup>-ir ultrasonic nebulizer, a portable device designed to deliver aerosols of different particle sizes by means of different baffle plates. This AC/DC powered and PCU controlled portable nebulizer ensures an optimum and reproducible deposition of medication via a pulsed mode delivery. The proposed dosing regimen is four times daily via oral inhalation.

**Questions for the Division:**

**PRECLINICAL DEVELOPMENT:**

1. Does the Division agree that the data from the 13-week inhalation toxicity studies in rats and dogs conducted under IND 70,362, coupled with the nonclinical data from previous intravenous and subcutaneous infusion studies contained in Remodulin<sup>®</sup> NDA 21-272, are sufficient to evaluate the potential chronic toxicity of treprostinil given via inhalation and that no further repeat-dose toxicity studies would be required to support an NDA for Treprostinil Sodium for Inhalation?
2. Does the Division agree that carcinogenicity studies with treprostinil would not be required to support an NDA for Treprostinil Sodium for Inhalation?
3. Does the Division agree that the three (3) preclinical studies summarized in the briefing package, plus completed data from the preclinical studies described in IND 70,362 and the preclinical data from the intravenous and subcutaneous infusion studies of Remodulin<sup>®</sup> discussed in NDA 21-272, will be sufficient to support an NDA for Treprostinil Sodium for Inhalation, 0.6mg/mL?

**Preliminary Response to questions 1-3:** Other than the need to evaluate the carcinogenic potential of remodulin when administered by the inhalational route of administration, the Division agrees that no further repeat-dose toxicity studies are needed to support an NDA.

Although the NIH IPAH registry from the 1980's showed a median survival of 2-3 years for PAH patients from time of diagnosis, the Division believes that this figure is not relevant today because of the availability of newer drug therapy. Better survival rates have been reported in the more recent literature (above 60% survival at 3 years in several studies; Sitborn et al., 2002, J. Am. Coll. Cardiol. 40: 780. 1-, 2-, 3- and 5 year survival rates of 85, 70, 63 and 55%, respectively, for drug-treated groups compared to 58, 43, 33 and 28% for historical controls). Because of these increased survival rates in PAH patients, and also in view of the treatment-related respiratory tract lesions observed in both rats and dogs in the 3-month inhalation studies, carcinogenicity studies are recommended to support an NDA.

**Discussion during Face to Face Meeting:** Dr Resnick confirmed that, other than the need to complete the carcinogenicity studies, the preclinical package is complete. Dr. Stockbridge noted that, should the sponsor seek approval restricted to a subpopulation refractory to other approved therapies and in which predicted survival is less than 3 years, the Division would consider waiving the carcinogenicity study requirement.

**CLINICAL DEVELOPMENT:**

1. The existing preclinical data, including a dog telemetry study, a hERG ion channel study, and a cardiac action potential assay in Rabbit Purkinje Fibers do not suggest that treprostinil exhibits an effect on the QT interval. In addition, the clinical data from the pre-and post-marketing Remodulin<sup>®</sup> SC and Remodulin<sup>®</sup> IV programs do not suggest that treprostinil exhibits an effect on the QT interval.

Assuming that the clinical data from the inhaled treprostinil program similarly do not suggest an effect on the QT interval, does the Division agree that a thorough clinical QT study is, therefore, not necessary?

**Preliminary Response:** We note that treprostinil was never assessed for its effect on QT. We do not consider the rabbit purkinje fiber assay and assessment of hERG ion channels as sufficient to allay concern about the ability of treprostinil to prolong repolarization. In order to assess the effect we need to have some idea as to what peak concentrations of treprostinil are generated by the inhalation route compared with subcutaneous and intravenous routes of administration, particularly the maximum concentrations to which the heart is exposed. We would recommend performing at least one study by the route that generates the highest concentrations. It may not be necessary to perform studies by different routes of administration to define the effects of treprostinil on repolarization.

**Lung Rx's Response received October 30, 2006:** Lung Rx would like clarification from the Agency regarding its preliminary response to the clinical development question #1 in relation a human QT study.

**Discussion during Face to Face Meeting:** The sponsor indicated that they understood that a thorough clinical QT study is needed. Dr. Stockbridge clarified that no additional studies would be needed if the sponsor could show that peak concentrations of treprostinil at the heart generated by the inhalation route are no higher than with subcutaneous and intravenous routes of administration. The sponsor indicated that they did not have any arterial data but to assess peak concentrations they proposed to assess arterial blood with the inhalation drug.

2. In the ongoing TRIUMPH-I clinical study, Lung Rx is using the NEBU-TEC OPTINEB<sup>®</sup>-ir mobile ultrasonic nebulizer, described in IND 70,362.

In the marketing application for Treprostinil Sodium for Inhalation, 0.6 mg/mL, Lung Rx intends to include in vitro performance data and open-label in-use patient acceptance data for an additional ultrasonic nebulizer.

Does the Division agree that this in vitro information and open-label in use patient data will be sufficient to support inclusion of an additional portable ultrasonic nebulizer operating in the pulsed delivery mode in the product label?

**Preliminary Response:** The Division agrees that this in vitro information and open-label in-use patient data will be sufficient to support inclusion of an additional portable ultrasonic nebulizer operating in the pulsed delivery mode in the product label.

**Lung Rx's Response received October 30, 2006:** Lung Rx would like clarification from the Agency regarding its expectations for the steps needed for the sale and use of more than one nebulizer for Treprostinil for Inhalation in the United States.

**Discussion during Face to Face Meeting:** Ms. Graham and Mr. Husband reconfirmed understanding that the sponsor plans to submit an application for a combination product with the inhalation drug only and that the sponsor will also include an additional portable ultrasonic nebulizer operating in the pulsed delivery mode in the product label. The sponsor added that they will provide all relevant data needed. The device components of the combination product will be regulated under the NDA.

3. A revised statistical analysis plan is included in the briefing package. Does FDA concur that Lung Rx has adequately addressed the statistical issues Agency raised in its June 8, 2006 letter to Lung Rx?

**Preliminary Response:** For a single pivotal trial, the evidence of efficacy needs to be at a level much smaller than 0.05 (two-sided). This takes into consideration the fact that the Division usually requires two positive well-controlled pivotal studies at level of 0.05 (two-sided) and that the approval of the drug for continuous percutaneous or IV route was based on a different metric (not 6MWT).

The analysis of the secondary endpoints needs to maintain the same overall alpha level as the primary efficacy analysis.

1. We discourage any interim analysis for the TRIUMPH I study. In addition, re-estimating sample size based on the estimated treatment effect at an interim analysis can compromise the study wise type I error rate and trial integrity. All discontinued patients need to be followed up for time to clinical worsening.
2. If the number of missing observations is not small, then the Agency may be led to conduct a sensitivity analysis using the most conservative "worst-case" scenario.
3. The DMB charter and CVs of the members need to be submitted.

**Lung Rx's Response received October 30, 2006:** Lung Rx has made the decision to omit the interim analysis in the TRIUMPH I study. Therefore, Lung Rx will continue enrolling patients until 220 patients are enrolled allowing for a 10% dropout rate giving 200 evaluable patients in the TRIUMPH I study. All discontinued patients will be followed up for time to clinical worsening. The statistical approach to type-I error control is already included into SAP that Lung Rx submitted to the Agency in its briefing package.

**We understand the Agency agrees that achieving a low p-value in the single TRIUMPH I study, powered to 90%, will be sufficient for an approval of the NDA for Treprostinil for Inhalation, 0.6 mg/mL.**

**Discussion during Face to Face Meeting:** The sponsor clarified that they will omit the interim analysis statistical approach in the TRIUMPH I study and asked that this can be discussed again at a later date. Additionally, they indicated understanding of the need to have a robust p-value with one study.

4. In addition to the drug-drug interaction studies that were already submitted in NDA 21-272 for Remodulin<sup>®</sup> SC and Remodulin<sup>®</sup> IV, United Therapeutics Inc., the owner of Lung Rx, Inc., conducted two clinical drug-drug interaction studies using an oral formulation of treprostinil diethanolamine, UT-15C. Specifically, the first study explored the potential interaction of bosentan with treprostinil and the other one evaluated the potential interaction of sildenafil with treprostinil.

Does the Division agree that these drug-drug interaction studies are sufficient to adequately explore the relevant drug-drug interactions?

**Preliminary Response:** No. Based on your in vitro metabolism data, treprostinil is metabolized primarily by CYP2C8 and to a lesser extent by CYP2C9. Consequently, you should conduct studies with inhibitors and inducers of these pathways to determine the magnitude of increase and decrease in treprostinil exposure upon co-administration; this evaluation will help in guiding treprostinil dose adjustment, if needed.

Orally administered treprostinil is likely to provide the most useful information. The recommended inhibitor for CYP2C8 is gemfibrozil and recommended inhibitors for CYP2C9 are fluconazole or amiodarone. In lieu of an interaction study with a CYP2C9 inhibitor, you may conduct a clinical study to compare the pharmacokinetics of poor metabolizers to extensive metabolizers, if appropriate. Metabolic induction of treprostinil via CYP2C8 and CYP2C9 pathways can be determined using rifampin. Please refer to the Draft Guidance for Industry- Drug Interaction Studies for additional information.

**Lung Rx's Response received October 30, 2006:** Lung Rx wishes to get clarification from the Agency on clinical development question #4 in relation to drug-drug interaction. The induction or inhibition of hepatic CYP2C8 or CYP2C9 by other drugs is anticipated to be of little or no importance for inhaled treprostinil as there is no compelling evidence that CYP2C8 or CYP2C9 is expressed in human lung [Klose 1999, Hukkanen 2001].

**Discussion during Face to Face Meeting:** Dr. Kumi agreed with the sponsor's proposal that a drug-drug interaction study would not be needed for inhaled treprostinil; however, this information is needed for oral treprostinil. In addition, he noted that acquiring the requested information is recommended as part of a comprehensive drug development program, irrespective of administration route.

5. As discussed in the briefing document, Lung Rx, Inc. believes it has incorporated plans to adequately address the following clinical issues, which were identified in the Division's June 8, 2006, letter concerning IND 70, 362 Amendment, Serial Number 0008.

- narrow dosing range;
- adequate benefit after intermediate term use;
- long-term persistence of drug effect
- oropharyngeal safety; and
- cardiac safety

Does the Division agree that Lung Rx has adequately addressed the clinical issues identified by the Agency in its June 8, 2006 letter to Lung Rx, Inc.?

**Preliminary Response:** The adequacy of the development plan would only partially be addressed.

We remain unconvinced that the dose range that you plan to study would adequately reflect the usable dose range of treprostinil by inhalation. The experience with subcutaneously administered drug suggests that dose constantly progresses upward over time of therapy. The explanation of this phenomenon is unclear. Your development program needs to address labeling recommendations for those having an inadequate response to inhaled medication.

The program you propose would give some information for intermediate term use, spanning the duration of the proposed study.

We are particularly concerned about the observations in rat studies where treprostinil by the inhalation route gave evidence of direct pulmonary toxicity and cardiac toxicity of unknown etiology. We may request a registry of patients with adequate follow up to assure that longer term treatment does not produce intolerable effects on these organs.

**Lung Rx's Response received October 30, 2006:** Lung Rx would like clarification from the Agency regarding its preliminary response about the adequacy of Lung Rx's development plan.

**Discussion during Face to Face Meeting:** Dr. Stockbridge indicated that the issue is not if the dose works but to be able to tell the patient what to do if the dose does not work. The sponsor confirmed that they would propose labeling to inform the patient that if the dose does not work they should move on to another therapy and not to increase the dosing of the drug. The Division was concerned that in addition to dose range, there should be adequate description as to the time course of benefit during the interdosing interval. The sponsor indicated that they would label their product accordingly and they indicated that there are no unblinding characteristics with this drug.

6. Based on the Division's prior experience with the other approved treprostinil sodium drug products for the treatment of PAH, does the Division agree that a single pivotal clinical study with robust statistical results for a clinically relevant primary endpoint, the peak six minute walk test, would provide sufficient confirmatory clinical evidence of effectiveness to support the marketing approval of Treprostinil Sodium for Inhalation, 0.6 mg/mL?

**Preliminary Response:** A marginal effect on 6-minute walk distance would not have support from other studies of treprostinil. We strongly suggest that you power for a lower p-value.

**Lung Rx's Response received October 30, 2006:** Lung Rx would like clarification from the Agency regarding its preliminary response to clinical development question #6 about powering the study for a lower p-value, specifically in relation to our response to clinical development question #3 above.

**Discussion during Face to Face Meeting:** Refer to clinical question #3.

**CHEMISTRY, MANUFACTURING AND CONTROLS:**

1. In order to increase its manufacturing capacity, United Therapeutics, Inc, the owner of Lung Rx, Inc., is outsourcing the treprostinil, API, described in NDA 21-272.

b(4)

However, by the first quarter of 2007, the manufacturing of treprostinil will be transferred to Silver Spring, Maryland.

Based on the CMC data in the Lung Rx's briefing package and those to be submitted in the forthcoming United Therapeutics's Prior Approval Supplement for NDA 21-272, the simplified treprostinil will provide API that meets the same acceptance criteria with a very similar impurity profile and similar acceptance criteria.

Does the Division agree that there is no need for any additional preclinical studies for this API?

**Preliminary Response:** The answer will depend on the outcome of the CMC review of the forthcoming United Therapeutic's Prior Approval Supplement for NDA 21-272 –

In general, any new impurities \_\_\_\_\_ above the ICH Qualification Threshold [ICH Guidance Q3B (R)], or higher levels of the currently known impurities than present in the non-clinical batch, may require appropriate toxicological evaluation prior to use in clinical trials.

b(4)

**Discussion during Face to Face Meeting:** There was no further discussion regarding this question.

2. Does the Division agree that the proposed acceptance criteria for the API and for the drug product Treprostinil Sodium for Inhalation, 0.6/mg/mL, are adequate to support an NDA application?

**Preliminary Response:** We cannot comment on acceptance criteria. This is covered during the review of the NDA.

**NOTE:** Refer to the Drug Product by its USAN designation, i.e. Treprostinil for Inhalation, 0.6 mg/mL (identical to how it is incorporated into the DP formulation) and not Treprostinil Sodium for inhalation, 0.6 mg/mL.

**Discussion during Face to Face Meeting:** There was no further discussion regarding this question.

3. Does the Division agree that for the purposes of process validation of the scaled-up batches of Treprostinil Sodium for Inhalation, 0.6 mg/mL, Lung Rx should use one lot of API manufactured using the original \_\_\_\_\_ process described in NDA 21-272 and one lot of API from each of the three sources \_\_\_\_\_ ?

b(4)

**Preliminary Response:** The Division agrees.

**Discussion during Face to Face Meeting:** There was no further discussion regarding this question.

4. Does the Division agree that the proposed in vitro performance testing scheme of the NEBU-TEC OPTINEB®-ir mobile ultrasonic nebulizer and that for an additional ultrasonic nebulizer made by a different manufacturer, with both ultrasonic nebulizers intended for the delivery of Treprostinil Sodium for Inhalation, 0.6 mg/mL, are adequate for the inclusion in the CMC section of the electronic NDA in the CTD format?

**Preliminary Response:** The Division agrees that the tests are adequate for inclusion in the NDA.

**Discussion during Face to Face Meeting:** There was no further discussion regarding this question.

5. Based on previous discussions with the Agency, Lung Rx, Inc., will carry out the 10 day in-use chemical stability and microbiological study of TRE in the ultrasonic nebulizer. Does FDA agree that such data would be sufficient to support the QID single day use of Treprostinil Sodium for Inhalation, 0.6 mg/mL, from a single LDPE — vial?

b(4)

**Preliminary Response:** The Division agrees that such data would be sufficient.

**Discussion during Face to Face Meeting:** There was no further discussion regarding this question.

**ADMINISTRATIVE QUESTIONS:**

1. Pursuant to FD&C Act, Section 506(a), (21 U.S.C.356), Lung Rx Inc. plans to submit to the Agency a formal request for the fast track designation for the development and approval and Treprostinil Sodium for Inhalation, 0.6 mg/mL. If the required criteria for such a designation are met, would the Division

have the available resources to review the appropriate sections of the "rolling" NDA submission of Treprostinil Sodium for Inhalation, 0.6 mg/mL?

**Preliminary Response:** We do not see how this drug for this indication falls under the purview for designation of fast track status. The indication sought is for a performance benefit, for which there are currently several other reasonable treatments approved.

We do not see a reason for a "rolling submission" for this NDA.

**Discussion during Face to Face Meeting:** There was no further discussion regarding this question.

2. The original NDA 21-272 for Remodulin<sup>®</sup> SC and Remodulin<sup>®</sup> IV was submitted in paper format. However the NDA for Treprostinil Sodium for Inhalation will be filed in e-CTD format. Does FDA prefer that the original preclinical, clinical and CMC data from NDA 21-272 and its NDA supplements be included in the electronic NDA or should all of that information be only cross-referenced in the new electronic NDA?

**Preliminary Response:** We prefer that you have all necessary information, including that of previous NDA submissions, in the single submission.

**Discussion during Face to Face Meeting:** There was no further discussion regarding this question.

Meeting recorder: \_\_\_\_\_  
John David

Meeting concurrence: \_\_\_\_\_  
Norman Stockbridge, M.D., Ph.D.

Draft: jd/11-7-06

Final: jd/11-13-06

RD:

Srinivasachar 11-9-06

Karkowsky 11-8-06

Freidlin 11-8-06

Kumi 11-8-06

Joseph 11-8-06

Resnick 11-8-06

Graham 11-9-06

Husband 11-9-06

Stockbridge 11-9-06

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

/s/

-----  
Norman Stockbridge  
11/14/2006 10:20:57 AM

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS  
FOOD AND DRUG ADMINISTRATION**



**US Mail address:**  
FDA/CDER/HFD-110  
5600 Fishers Lane  
Rockville, MD 20857

Woodmont II  
1451 Rockville Pike  
Rockville, MD 20852

**This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCRDP (HFD-110); 5600 Fishers Lane; Rockville, MD 20857**

**Transmitted to FAX Number:** (301) 608-9291

**Attention:** Mr. Ted Staub

**Company Name:** Lung Rx, Inc,

**Phone:** (301) 608-9292 ext 1029

**Subject:** **April 26, 2005 Recommendations following 30  
Day Safety Meeting T-con Minutes  
IND 70, 362**

**Date:**

**Pages including this sheet:**

**From:** LCDR John David  
**Phone:** 301-594-5309  
**Fax:** 301-594-5494

**PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

Minutes of a telecon between Lung Rx, Inc. and the FDA Division of Cardio-Renal Drug Products

Sponsor: Lung Rx, Inc.  
Drug: Treprostinil Sodium for Inhalation  
IND: 70,362  
Date of request: April 21, 2005  
Date request received: FDA Requested  
Date of confirmation: April 21, 2005  
Date of meeting: April 26, 2005  
Time: 2:30 – 3:30 pm

Type/Classification: Type B/Pre-IND: Recommendations following 30 Day Safety Meeting

Meeting Chair: Abraham Karkowsky, M.D., Ph.D.

Meeting recorder: John David

FDA Participants:  
Abraham Karkowsky, M.D., Ph.D. Acting Deputy Director, Division of Cardio-Renal Drug Products, HFD-110  
John David Regulatory Health Project Manager, HFD-110

Lung Rx, Inc. Participants:

b(4)

Robert Roscigno President and COO, Lung Rx  
Ted Staub Sr. Director, Clinical Development, and Project Leader

Background:

Treprostinil is the active ingredient of Remodulin™, approved for both subcutaneous and intravenous infusion and currently marketed by United Therapeutics Corporation (UTC) for the treatment of pulmonary arterial hypertension. LungRx, Inc., a subsidiary of UTC, is presently developing Treprostinil Sodium Solution for Inhalation packaged in ampoules. This original IND application is proposing to use Treprostinil Sodium Solution for Inhalation for the purpose of treating pulmonary arterial hypertension patients.

OPTINEB®-ir Microprocessor-Controlled Mobile Ultrasonic Nebulizer, an ultrasonic inhalation device manufactured by Nebu-Tec, will be used for pulmonary administration of Treprostinil Sodium Solution for Inhalation in the proposed clinical study.

Introductions

Dr. Karkowsky provided the following Division recommendations to the Sponsor:

Medical

1. Re-submit the protocol updated with the recommended changes.
2. Clarify the choice of doses of treprostinil chosen for this study.

3. Consider employing a dose-ranging study. At the minimum allow for higher doses during the open-label portion of the study.
4. Define the treatment algorithm for those who deteriorate on the combination of bosentan and treprostinil inhalation.
5. Clarify when peak and trough measurements of walking distance are performed relative to the bosentan dose. At the minimum capture the time of exercise performance at baseline and on-treatment relative to the last dose of bosentan and treprostinil.
6. Add safety assessments for oropharyngeal examination at each visit.
7. Perform visual oropharyngeal evaluations at each visit and provide criteria for recommendation for complete ENT exam.
8. Treprostinil is administered asymmetrically during the day. Clarify during which trough measurements will be taken. Also clarify the timing of when measurements will be made relative to the bosentan peak and trough level.
9. Since there is the possibility of withdrawal at the inter-dosing interval, the time relative to the last dose of treprostinil should be captured for any adverse event possibly related to deterioration.

#### Chemistry

1. Since the reservoir volume of treprostinil for inhalation is sufficiently large, for multiple day administration, extend the microbiology testing to 10 days – Dr. Cooper previously discussed this issue with the Sponsor (Ted Staub) and he agreed that the calculations included in the cover letter were in error.
2. The clinical protocol proposes device use of 6 and 9 breaths per dosing interval (with 4 doses per day -- 0, 4, 8, and 12 hours). However, the in-use stability data, delivered dose data, and particle size data were provided for device use of 3 breaths per dosing interval. Please provide these data for 9 breaths per dosing interval over 24 hours at or before the time of NDA filing.
3. The Sponsor can continue to perform the study with a nebulizer that has been adequately validated to deliver the proposed drug. The sponsor should be aware of the consequences of using an unapproved device.
4. Any device used should be specifically validated for delivery of treprostinil.

#### Pharmacology

1. Do assessment (exams) and monitoring of patient's oral and pharyngeal mucosa for lesions.
2. **Do ECG's concomitantly.**
3. Assess the peak drug effect on vital signs also during the inhalation.
4. Correct all typos in the Pharm/Tox section - (Vol. 3, pages 4 to 32, especially replacing  $\geq$  symbol with units of dosage (mg,  $\mu$ g etc.)

#### Biopharmaceutics

1. Perform sparse PK sampling so that PK/PD can be analyzed to benefit future studies.
2. Provide more details on the times of the PK blood samples. Capture early time points relative to the inhalation.
3. Collect arterial blood concentrations as more reflective of pulmonary exposure.
4. Additionally, since bosentan is an inducer of CYP3A4, 2C9, and possibly 2C19, while treprostinil is metabolized hepatically (specific enzymes unknown) then the sponsor should perform a drug-drug interaction study with bosentan. Relevant concentrations of treprostinil should be achieved in this study.
5. Perform a QT study.
6. Capture early kinetic time points (after inhalation at 1, 5, 10 and 15 minutes).
7. Provide some assessment of arterial concentrations after inhaled treprostinil would be of interest.

Statistics

1. Submit a Special Protocol Assessment including a detailed Statistical Analysis Plan (SAP). The SAP should be submitted to the IND well before most of the patients received their first dose of study drug.
2. If the sponsor plans to show the results for the three measurements of the 6MWT (peak, trough and immediately after the first dose) in the labeling, then a hierarchy for testing the three co-primary endpoints or other procedure for maintaining the overall alpha level of 0.05 should be pre-specified in the SAP.
3. If the sponsor plans to show the results for the secondary endpoints in the labeling, then a hierarchy for testing the secondary endpoints or other procedure for maintaining the overall alpha level of 0.05 should be pre-specified in the SAP.
4. The primary efficacy population should be clearly defined in the SAP. A conservative imputation method for missing primary efficacy measurements should be explicitly pre-specified in the SAP. A sensitivity analysis should be pre-specified in the SAP to demonstrate the robustness of the primary efficacy results.
5. Every effort should be made to follow up discontinued patients for the primary endpoint and those secondary endpoints that the sponsor plans to show in the labeling.
6. SAP should include all details on the ANCOVA model for the primary efficacy analysis (e.g., the categories in the PAH etiology, pooling of small centers, if any, etc.).
7. A trough 6MWT is defined as a walk prior to or no less than 4 hours post study drug inhalation. What about the other trough prior to inhalation at 0 hour after the 12 hour interval?
8. SAP should provide a detailed description of the statistical method separately for each endpoint.
9. Instead of replacing discontinued patients, we recommend planning to randomize a larger number of patients to account for discontinuations.
10. The Sponsor is reminded that one study with a p-value close to 0.05 will not be sufficient. The usual standard for strength of evidence is two positive studies with  $p < 0.05$  in each study.

Meeting recorder: \_\_\_\_\_  
John David

Meeting concurrence: \_\_\_\_\_  
Abraham Karkowsky, M.D., Ph.D.

Draft: 5/6/05  
Final: 5/6/05

RD:  
Karkowsky 5/6/05

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

/s/

-----  
Abraham Karkowsky  
5/9/05 04:27:05 PM

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS  
FOOD AND DRUG ADMINISTRATION**



**US Mail address:**  
FDA/CDER/HFD-110  
5600 Fishers Lane  
Rockville, MD 20857

Woodmont II  
1451 Rockville Pike  
Rockville, MD 20852

**This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCRDP (HFD-110); 5600 Fishers Lane; Rockville, MD 20857**

**Transmitted to FAX Number:** (301) 608-9291  
**Attention:** Mr. Ted Staub  
**Company Name:** Lung Rx, Inc,  
**Phone:** (301) 608-9292 ext 1029  
**Subject:** December 16, 2004 Pre-IND Meeting Minutes  
IND 70, 362  
**Date:**  
**Pages including this sheet:**

**From:** LCDR John David  
**Phone:** 301-594-5309  
**Fax:** 301-594-5494

**PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

Meeting minutes between Lung Rx, Inc. and the FDA Division of Cardio-Renal Drug Products

Sponsor: Lung Rx, Inc.  
Drug: Treprostinil Sodium for Inhalation  
IND: 70,362  
Date of request: October 18, 2004  
Date request received: October 20, 2004  
Date of confirmation: October 26, 2004  
Receipt date of briefing package: November 15, 2004  
Date of meeting: December 16, 2004  
Type/Classification: Type B/Pre-IND

Meeting Chair: Norman Stockbridge, M.D., Ph.D.  
Meeting recorder: John David

FDA Participants:

Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical Officer, HFD-110
Nhi Beasley, Pharm.D.	Acting Team Leader, Biopharmaceutics, HFD-860
Anthony Proakis, Ph.D.	Pharmacologist, HFD-110
Kasturi Srinivasachar, Ph.D.	Chemistry Team Leader, HFD-110
Ann Graham	Acting Branch Chief, HFZ-480
Michael Husband	Medical Devices Consultant, HFZ-480
John David	Regulatory Health Project Manager, HFD-110
Denise Hinton	Regulatory Health Project Manager, HFD-110

LungRx Participants:

Dr. Robert Roscigno	Sr. Vice President
Ted Staub	Sr. Director, Clinical Development
Teresa Bongartz	Vice President, Medical Relations

Attending on behalf of LungRx:

b(4)

Background:

Lung Rx, Inc. requested a meeting with the Agency to discuss the development program for Treprostinil Sodium for Inhalation and to seek concurrence and guidance on the post IND plan regarding Pharmacology/Toxicology, CMC, investigator sponsored work performed to date, the content and timing of IND filing, and Clinical Trials.

The proposed indication for Treprostinil Sodium is the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. However, Bosentan labeling currently indicates it has not been studied in patients with either chronic HIV or chronic thromboembolic disease. Delivery of the drug is by OPTINEB®-ir a portable device designed to deliver aerosols of different particle sizes by means of different baffle plates. A 510(k) application was submitted in November 2004 to CDRH for the device.

**Discussions:**

b(4)

Following introductions, the Sponsor opened the meeting by demonstrating the use of the OPTINEB-ir ® ultrasonic nebulizer in the delivery of Treprostinil Sodium for Inhalation and clarified that the selected dose is 45µg /dose (9 breaths); 180µg /day assuming q.i.d. dosing for the TRIUMPH I trial. The Sponsor explained that the chamber is filled with 3 ml of contact solution. The device will deliver 4 doses during a day and the power source is a snap-on battery pack with a car or home adapter. The number of inhalations is programmed and an inhalation signal alerts patients when to inhale.

The Division expressed concern over the absence of a lockout feature to control whether the device will deliver inhalation with or without the patient. There is also the potential that patients, in an effort to save money, may not throw out the residual remaining in the chamber, thus resulting in the patient receiving an incorrect dose. In response to the Division's concerns and question of what is the volume of the dose cup, the Sponsor responded that the information regarding the volume of the cup would be provided at a later date and noted that the cups are disposable and the patients will be told that the cup and filter need to be changed daily. In order for the device to perform correctly, the minimum volume in the dose cup is required to form a cloud and the Sponsor stated that it is specifically written that the residual is to be thrown out after the fourth dose. Microbiology tests have shown no growth after the third day.

In regard to dosing, the Division asked if the first and fourth dose delivered were equal and stressed the importance of making sure the delivered dose is the same for all administrations. This is not an IND issue, but one that would need to be addressed and resolved before an NDA action. In addition, it is important to have information on drug disposal, stability, and microbial growth in order to determine how strongly product labeling should be written to encourage disposal of the drug remaining in the dose cup after four doses or one day's use. Chemical stability and the amount of drug delivered at the mouthpiece should also be measured at interim time points; however, the 24-hour data presented is acceptable for the IND. The Sponsor confirmed that the second dose is equal to the first, but was unsure about the fourth dose. They concurred with the Division's recommendation to consider the realities of patient use and agreed to do the following:

- extend microbiology testing to 10 days for the fluid and filter
- assess drug stability in dose cup beyond 24 hours
- assess linearity of dose with intermediate time points for chemical stability

The Division acknowledged the Sponsor's concern over the difficulty in testing failure analysis. It will be acceptable to identify failure points as it will measure output, but not necessarily explain the reason for the occurrence.

**The Division responded to the Sponsor's questions as follows:**

**Pharmacology/Toxicology:**

- 1) Does FDA agree that the current Pharmacology/Toxicology studies support the initiation of the proposed clinical trial in February/March 2005?

**FDA response: It was confirmed that Lung Rx does have right of reference to the animal pharmacology/toxicology information in the Remodulin NDA, as they are a subsidiary of United Therapeutics.**

The Division stated that the proposed 3-month (bridging study)/2 species testing data are sufficient for this IND; however after reviewing the reference data and further guidance on the requirements for the proposed route for chronic use for the marketing application, the Sponsor will be contacted if any other chronic animal data are necessary for the NDA.

There was a brief discussion about the concentration of drug in the venous flow ( $C_{max}$ ) and whether safety could be assumed even if the  $C_{max}$  in the inhaled product was not higher given the higher exposures in the heart from Treprostinil levels directly from the lungs without systemic dilution. The Sponsor assumed that the maximum is possibly not as high for the following reasons: 1) delivery of material cannot be calculated, 2) there were no observed change in systemic blood pressure in those patients that have been studied in Giessen and in a clinic at UCSD, or 3) there was some delay of entry into circulation. The Division indicated that the animal study data should provide the necessary information.

The Sponsor was asked to explain how they intend to address the potential safety issues associated with the expected higher  $C_{max}$  levels of Treprostinil than seen in the S.C. or I.V. products. They explained that surprisingly the  $C_{max}$  values are higher and measured the data from the Giessen exposures as well as those estimated for the proposed clinical trial as compared to the  $C_{max}$  in the Remodulin approved labeling. The Sponsor anticipated that the AUC would be far less, but the  $C_{max}$  was unexpectedly higher (see attachment 1) and led them to select 45µg q.i.d /9 breaths as the appropriate dose. They also presented data indicating that the  $C_{max}$  values following inhalation were similar to the  $C_{ss}$  (steady state concentration) values observed following continuous subcutaneous administration.

The Division referred to the " $C_{max}$  Power Point Slide" (attachment 1) and asked the Sponsor to explain if the assay is the same in the way concentrations were measured and to define NC. The Sponsor stated that the assay is the same and NC means not calculated. The clearance/F values on the slide suggested that inhaled bioavailability is approximately 50% of the SC product. LungRX agreed with the Division's advice to follow the CFR requirement and conduct a single study looking at the relative bioavailability for routes of the proposed formulation versus the approved route (preferably, IV) of the reference product.

- 2) Based on the inhalation work performed to date and the additional studies that were part of the Remodulin NDA and will be referenced in the IND and NDA for Treprostinil Sodium for Inhalation, does FDA agree that there will be no need to do further toxicology studies in support of an NDA for Inhalation?

**Response:** As discussed above, the Division will provide additional guidance for an NDA in regards to chronic toxicity animal data requirements for the inhaled route of administration after a review of proposed IND data and the Remodulin animal toxicology data.

#### CMC

- 1) Does FDA agree that the CMC information provided in the briefing document is adequate to support the initial IND?

**FDA response:** The Division agrees that the provided documentation is adequate to support the IND, as the Sponsor confirmed that they will cross reference the approved NDA for drug substance. They explained that the stability study was done with different humidity because of the semi-permeable container.

The Division informed the Sponsor that it is acceptable to have 24-hour stability for the IND and asked them to provide stability data at four intermediate time points and measure the amount delivered by the mouth piece. There are no CDRH concerns with regard to CMC that would prohibit the IND from going forward.

- 2) LungRx is planning to use the OPTINEB-ir ® ultrasonic nebulizer in the planned clinical study. A 510(K) application has been submitted by NEBU-TEC, the nebulizer device manufacturer, to FDA on April 30, 2004. LungRx will provide an authorization letter from NEBU-TEC to reference this device application in the IND. Is this plan acceptable to FDA?

**FDA response:** Ms. Graham (CDRH) stated that the plan may be sufficient for the IND, but will have to be re-assessed when the NDA is submitted.

- 3) LungRx is planning to use single-dose low-density polyethylene ampoules containing 3.0 mL of sterile treprostinil sodium solution (0.6 mg treprostinil/mL) for the planned clinical study. The study patients will be instructed to empty the contents of one ampoule into the nebulizer reservoir and then use the nebulizer four times (at 0, 4, 8, and 12 hours) in a 12-hour period according to the instruction provided by the clinic site. At the end of the 12 hour-period, the patients will clean the reservoir according to the instructions provided to them by the clinic site. An in-use stability study will be performed to confirm that the solution has satisfactory stability for up to 24 hours in the nebulizer dose cup. Additionally, results of a microbial challenge test performed using several organisms showed that the product does not support microbial growth. Details of the in-use stability study and the microbial challenge test will be provided in the IND. Is this administration plan acceptable to FDA?

**FDA response:** As previously discussed, additional information needs to be provided in order for the administration plan to be acceptable. The Division asked why a single dose level is proposed instead of a range of doses or a dose titration scheme like the SC product to be able to adjust dose in order to achieve an effect. The Sponsor indicated that dosing was based on achieving an effect and on side effects (toxicities). Adverse events related to the drug and the reason for the titration of the dose were because they cannot immediately start a patient on an effective dose of IV drug, as the patient would not tolerate it acutely. Furthermore, with this route, no rate limiting effects were identified but they did find a range for therapeutic effect. Early on, they went to the highest dose of toxicity and it resulted in adverse events. b(4)

The Sponsor further rationalized that the SC or IV drug is dosed until either toxicity or efficacy is reached but with the inhaled product the narrow range of treatment effect from investigator studies in Glissen and UCSD appears to be higher than 15 µg q.i.d. and somewhere around 30 to 45 µg q.i.d and thus it appears that an effective dose could be administered immediately.

The Sponsor responded to the question of why they believed a plateau had been reached in the dose response curve by stating that the dose might be capable of being higher than 45 µg q.i.d if necessary, before reaching dose-related toxicity. They also noted that there is an acute vasodilatory effect and spillover if the dose is titrated up, and based this on studies in which side effects were noticed at doses of i. Therefore, they believed that the level is too high and that 45 µg is the best dose. b(4)

The Division noted that over time, the patients on the SC product required a higher dose of drug; therefore, a patient on the inhaled product may also need more drug over time which could pose a problem. The Sponsor indicated that the preliminary acute and chronic data support the 45-µg dose, but that it cannot be ruled out that over time a greater dose might be necessary for some patients. The Sponsor responded that all three of the compassionate-use patients being assessed have been on the

drug for 10 to 11 months and have been maintained on a consistent dose, and that based on the admittedly limited experience, the need for dose escalation in some patients simply may not appear as an issue with the inhalation product.

Clinical

1) Does FDA agree that the investigator sponsored information is sufficient to allow the start of a clinical trial of approximately n=120?

**FDA response:** The Division stated the need to understand the following:

- 1) Time course effect after dose (benefit).
- 2) Effect of dose (clear rationale to inform people in labeling as to why only one dose is needed).
- 3) Is the effect seen after the first dose the same as after 3 months of dosing.
- 4) Is there a safety issue associated with withdrawing the drug after 24 hours (i.e., the effects of 12 hours on drug and then 12 hours off drug). Dr. Stockbridge noted that data from 8 patients is not variable enough, and that controlled placebo data and a reasonable safety database will be needed.

The Sponsor clarified that the study population are patients who are on Bosentan, meet the label indications, and are symptomatic. The Division advised them to exclude patients if they are not on a marketed label indication for Bosentan. For the 6-minute walk test (6MWT), the Division asked when this was to be measured and the Sponsor explained that data from trough would be looked at and that it was anticipated that a patient would have an additional 30-meter improvement on top of Bosentan. In regard to ETT as function of time after dose, the Division stated it would be necessary to show effectiveness throughout dosing interval. If it is not, then patients will need to be informed of what to expect.

The Division suggested that the primary analysis of the primary endpoint in TRIUMPH I should be a peak measurement, with the trough measurement, an additional primary analysis of the primary endpoint only if the peak analysis is positive and finally that a 6MWT after the first dose after randomization should also be pre-specified in the statistical analysis plan as yet the next primary analysis of the primary endpoint, possibly to support intermittent/sporadic use. The Sponsor needs to plan and rank secondary endpoints in an alpha-conserving manner. Dr. Stockbridge noted that the we agree with the non-parametric analysis presented, but the statisticians will ask to see additional details, including how the Sponsor proposes to handle withdrawals.

The Division indicated that a single study would address whether a single trial of  $p < 0.05$  on the primary endpoint by the pre-specified primary analysis would be sufficient in an NDA to demonstrate substantial evidence of effectiveness.

2) Does FDA agree with the design of the proposed clinical trial?

**Response:** In addition to the above discussion, the Division asked about the effects of Treprostinil on QT interval, and suggested the need for the Sponsor to conduct a definitive QT study on the effects of Treprostinil on cardiac electrophysiology. The Sponsor stated that they would get back to us on the details of a QT study as theirs is not as definitive as written in the ICH Guidance. They noted that no approved drug for PAH has reported any such study in its approved labeling and that the only drug being studied for PAH that has such a study reported in the public domain is on Viagra and that is only because Bayer included a Viagra control arm in its definitive QT study on Levitra for erectile dysfunction. The Division does not object to seeing this data, regardless of who sponsored the study. The Sponsor noted that to their knowledge, none of the 250 orphan drugs approved by FDA had a definitive QT study conducted at the time of approval. Dr. Stockbridge did not think that the orphan

drug status of inhaled Treprostinil for PAH would be determinative as to whether such a study would be needed. The Division asked how much drug is delivered to the heart because it may affect ECG's. The Sponsor responded that assessing other organs (airway) may provide more information.

The Division mentioned that given the possibility that this drug may move to a new review Division after CDER reorganizes, the Sponsor may need to assess airway resistance and spirometry. They were asked if subjects with bronchospastic disease would be excluded and answered that they would not be excluded. CDRH questioned whether Bosentan was the only drug a subject would be taking. The Sponsor noted that subjects might be on other medications including inhaled bronchodilators for coexistent obstructive airways disease. Patients with PH due to lung disease, however, they would be excluded since they do not have a label indication for Bosentan. Young patients will be enrolled in TRIUMPH I; however, age will be limited to that approved in the Bosentan labeling. The Division also questioned what data could be put together with respect to exposure-response relationship. LungRX replied that there was some exposure-response relationship provided to FDA with Remodulin.

#### Summary of Main Action Items (Lung Rx, Inc.)

The Agency recommended that Lung Rx, Inc. do the following:

1. Extend microbiology testing to 10 days for the fluid and filter
2. Provide stability data of the drug in the dose cup after 24 hours.
3. Assess linearity of dose with intermediate time points for chemical stability.
4. Conduct a study to describe the relative bioavailability of their product given via inhalation compared to the reference approved standard.
5. Cross reference the drug against approved drugs.
6. Provide stability data at four intermediate time points and measure the amount delivered by the mouth piece.
7. Provide a detailed statistical plan that provides detailed information distinguishing secondary endpoints by benefit and in an alpha-conserving manner.
8. Provide data on: 1) time course affect after dose (benefit), 2) effect of dose (clear rationale to inform people in labeling), 3) the effect seen after the first dose and whether effect is the same after 3 months, 4) safety associated with withdrawal of drug after 24 hours, 5) the details of patients enrolled in TRIUMPH I study, and 6) provide 6MWT measurement data.
9. Provide QT study data on the effects of Treprostinil on cardiac electrophysiology.

Meeting recorder: \_\_\_\_\_  
John David

Meeting concurrence: \_\_\_\_\_  
Norman Stockbridge, M.D., Ph.D.

Draft: 1/5/05  
Final: 1/13/05

RD:  
 Hinton 1/5/05  
 Fromm 1/6/05  
 Beasley 1/7/05  
 Srinivasachar1/11/05  
 Proakis 1/11/05  
 Karkowsky1/12/05  
 Stockbridge 1/12/05

Attachment 1

	Dosing Regimen	Daily Dose mcg	Cmax ng/mL	AUC hr*ng/mL	CL mL/min/kg
Label	9.3 ng/kg/min	937	2	48	4.6
Giessen	0.84 mcg/kg	58.8	1.8	1.72	9.3
(n=15)	(0.24-2.08)	(16.8-145.6)	(0.59-4.57)	(0.73-3.94)	(2.5-24.1)
Proposed	45 mcg qid	180	NC	4.66	9.3
Dose			1.39*	1.16	9.3

Arithmetic Mean (Range)

\*predicted single dose Cmax

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

/s/

-----  
Norman Stockbridge  
1/13/05 04:01:48 PM

## ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 22-387 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Tyvaso Established/Proper Name: treprostinil Dosage Form: Inhalation Solution		Applicant: United Therapeutics Agent for Applicant (if applicable):
RPM: Daniel Brum, PharmD, MBA, RAC		Division: Division of Cardiovascular and Renal Products
<p><b>NDA:</b>                      NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2)                      Efficacy Supplement:    <input type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b>                      Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</b></p> <p><input type="checkbox"/> No changes                      <input type="checkbox"/> Updated                      Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p> <p><b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b></p>
❖ User Fee Goal Date Action Goal Date (if different)		7/30/09
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions ( <i>specify type and date for each action taken</i> )		<input checked="" type="checkbox"/> None
❖ Advertising ( <i>approvals only</i> ) Note: If accelerated approval (21 CFR 314.510/601.41), advertising MUST have been submitted and reviewed ( <i>indicate dates of reviews</i> )		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application <sup>2</sup> Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 5  <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC  NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies  <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC  Comments:	
❖ Application Integrity Policy (AIP) <a href="http://www.fda.gov/ora/compliance_ref/aip_page.html">http://www.fda.gov/ora/compliance_ref/aip_page.html</a>	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• If yes, exception for review granted ( <i>file Center Director's memo in Administrative/Regulatory Documents section, with Administrative Reviews</i> )	<input type="checkbox"/> Yes
• If yes, OC clearance for approval ( <i>file communication in Administrative/Regulatory Documents section with Administrative Reviews</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Date reviewed by PeRC ( <i>required for approvals only</i> ) If PeRC review not necessary, explain: <input checked="" type="checkbox"/>	Orphan designation exemption
❖ BLAs only: RMS-BLA Product Information Sheet for TBP has been completed and forwarded to OBPS/DRM ( <i>approvals only</i> )	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Press Office notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new RMS-BLA Product Information Sheet for TBP must be completed.

❖ Exclusivity		
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes	
<ul style="list-style-type: none"> <li>NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes If, yes, NDA/BLA # 21-272 and date exclusivity expires: 5/21/09	
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:	
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:	
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:	
<ul style="list-style-type: none"> <li>NDA only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date 10-year limitation expires:	
❖ Patent Information (NDAs only)		
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.	
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)	
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire	
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For each <b>paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified	

- [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for each paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
<b>CONTENTS OF ACTION PACKAGE</b>	
❖ Copy of this Action Package Checklist <sup>3</sup>	7/29/09
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/nonconsent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) 7/30/09
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
❖ Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	7/29/09
❖ Original applicant-proposed labeling	6/30/08
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	Remodulin (treprostinil) SC/IV, Ventavis (iloprost)
❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> None

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 5/29/08

❖ Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	7/29/09 (PPI & IFU)
❖ Original applicant-proposed labeling	6/30/08 (IFU only, no PPI)
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	Ventavis (iloprost)
❖ Labels (full color carton and immediate-container labels) (write submission/communication date at upper right of first page of each submission)	
❖ Most-recent division proposal for (only if generated after latest applicant submission)	
❖ Most recent applicant-proposed labeling	7/22/09
❖ Labeling reviews (indicate dates of reviews and meetings)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEDP <input checked="" type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews (e.g., RPM Filing Review <sup>4</sup> /Memo of Filing Meeting) (indicate date of each review)	Filing Review 11/14/08; RPM overview 7/29/09
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> <li>• Center Director's Exception for Review memo</li> <li>• If approval action, OC clearance for approval</li> </ul>	<input checked="" type="checkbox"/> Not on AIP
❖ Pediatric Page (approvals only; must be reviewed by PERC before finalized)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (include certification)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies <ul style="list-style-type: none"> <li>• Outgoing communications (if located elsewhere in package, state where located)</li> <li>• Incoming submissions/communications</li> </ul>	Approval letter 7/28/09
❖ Postmarketing Commitment (PMC) Studies <ul style="list-style-type: none"> <li>• Outgoing Agency request for postmarketing commitments (if located elsewhere in package, state where located)</li> <li>• Incoming submission documenting commitment</li> </ul>	<input type="checkbox"/> None 7/28/09
❖ Outgoing communications (letters (except previous action letters), emails, faxes, telecons)	9/3/08: filing letter with issues 11/20/08: micro IR letter 1/13/09: CMC IR letter 3/3/09: Device/Labeling IR Letter 3/13/09: t-con with sponsor (device) 3/17/09: t-con with sponsor (device) 3/30/09: t-con with sponsor (device)

<sup>4</sup> Filing reviews for other disciplines should be filed behind the discipline tab.  
Version: 5/29/08

	5/22/09: meeting minutes
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Pre-Approval Safety Conference ( <i>indicate date; approvals only</i> )	<input checked="" type="checkbox"/> Not applicable
• Regulatory Briefing ( <i>indicate date</i> )	<input checked="" type="checkbox"/> No mtg
• Pre-NDA/BLA meeting ( <i>indicate date</i> )	<input type="checkbox"/> No mtg 5/16/08
• EOP2 meeting ( <i>indicate date</i> )	<input checked="" type="checkbox"/> No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/25/09; 7/28/09
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 7/27/09; 4/19/09
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	TL is the primary reviewer
• Clinical review(s) ( <i>indicate date for each review</i> )	4/3/09
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Safety update review(s) ( <i>indicate location/date if incorporated into another review</i> )	see medical review
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	see medical review
❖ Clinical reviews from other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None QT review 1/30/09
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not needed
❖ REMS	<input checked="" type="checkbox"/> None
• REMS Document and Supporting Statement ( <i>indicate date(s) of submission(s)</i> )	
• Review(s) and recommendations (including those by OSE and CSS) ( <i>indicate location/date if incorporated into another review</i> )	
❖ DSI Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested
• Clinical Studies	1/8/09; 4/23/09
• Bioequivalence Studies	n/a
• Clinical Pharmacology Studies	n/a
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None

<sup>5</sup> Filing reviews should be filed with the discipline reviews.  
Version: 5/29/08

Clinical Microbiology Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None 4/7/09
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 4/7/09
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 3/24/09
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 3/24/09
❖ DSI Clinical Pharmacology Inspection Review Summary	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 3/25/09
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 3/25/09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 4/28/08 (IND 70,362) Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary	<input checked="" type="checkbox"/> None requested
<b>CMC/Quality</b> <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/TeamLeader Review(s) (indicate date for each review)	<input type="checkbox"/> None 3/24/09; 4/27/09; 7/23/09; 7/28/09
• CMC/product quality review(s) (indicate date for each review)	<input type="checkbox"/> None 3/23/09; 7/23/09
• BLAs only: Facility information review(s) (indicate dates)	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	3/23/09 <input type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date for each review)	<input type="checkbox"/> None CDRH 4/1/09; 6/10/09
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	3/24/09 (see CMC review)
<input type="checkbox"/> Review & FONSI (indicate date of review)	
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	

❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> <li>• NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i></li> </ul>	Date completed: 12/1/08 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> <li>• BLAs:               <ul style="list-style-type: none"> <li>➤ TBP-EER</li> <li>➤ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i></li> </ul> </li> </ul>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed

## Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

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

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

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

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

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

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

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

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

---

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

---

*/s/*

---

DANIEL BRUM  
07/29/2009