CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-866

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

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

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/10
See OMB Statement on Page 3.

NDA NUMBER
20-866

NAME OF APPLICANT/NDA HOLDER
VeroScience LLC

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)
CYCLOSET

ACTIVE INGREDIENT(S)	STRENGTH(S)
bromocriptine mesylate	0.8 mg

DOSAGE FORM
Tablet

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	b. Issue Date of Patent	c. Expiration Date of Patent
5,716,957	2-10-1998	2-10-2015

d. Name of Patent Owner		
VeroScience LLC and The Board of Supervisors of Louisiana State University and Agricultural and Mechanical College	Address *(of Patent Owner)* 1334 Main Road	
	City/State Tiverton/RI	
	ZIP Code 02878	FAX Number *(if available)* (401) 816-0524
	Telephone Number (401) 816-0523	E-Mail Address *(if available)* contact@veroscience.com

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) ☞ Not applicable.		
	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

. 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

504

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 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, 2, 4-6 and 8	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.)* Improvement of glycemic control. Claims 1, 2, 4-6 and 8. Labeling sections 1.1, 1.2, 11, 12.1, 12.2, 14, 14.1, 14.2, 17.3

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

505

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 04/04/2008

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.

☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name S. Peter Ludwig	
Address Darby & Darby P.C. 7 World Trade Center, 250 Greenwich Street	City/State New York/NY
ZIP Code 10007	Telephone Number (212) 527-7770
FAX Number *(if available)* (212) 527-7701	E-Mail Address *(if available)* pludwig@darbylaw.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

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Department of Health and Human Services
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NAME OF APPLICANT/NDA HOLDER
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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)
CYCLOSET

ACTIVE INGREDIENT(S)	STRENGTH(S)
bromocriptine mesylate	0.8 mg

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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,679,685	10-21-1997	10-21-2014

d. Name of Patent Owner		
VersoScience LLC and Geneva Pharmaceuticals, Inc.	Address *(of Patent Owner)* VeroScience LLC	
	City/State Tiverton/RI	
	ZIP Code 02878	FAX Number *(if available)* (401) 816-0524
	Telephone Number (401) 816-0525	E-Mail Address *(if available)* contact@veroscience.com

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)		
☞ Not applicable.	Address *(of agent or representative named in 1.e.)*	
	City/State	
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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

507

PSC Graphics (301) 443-1090 EF

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 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.

Not applicable.

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)

.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?	☐ 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

or 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

508

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.***

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☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name S. Peter Ludwig	
Address Darby & Darby, P.C. 7 World Trade Center, 250 Greenwich Street	City/State New York, NY
ZIP Code 10007	Telephone Number (212) 527-7770
FAX Number *(if available)* (212) 527-7701	E-Mail Address *(if available)* pludwig@darbylaw.com

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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,468,755	11-21-1995	11-21-2012

d. Name of Patent Owner		
The Board of Supervisors of Louisiana State University and Agricultural and Mechanical College	Address *(of Patent Owner)* Louisiana State University, Office of Intellectual Property, 203 Boyd Hall	
	City/State Baton Rouge/LA	
	ZIP Code 70803	FAX Number *(if available)* (225) 615-8965
	Telephone Number (225) 615-8967	E-Mail Address *(if available)* oip@lsu.edu

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)		
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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

510

PSC Graphics (301) 443-1090 EF

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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, 2, 4, 6, 8-14, 17-29	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.)*

(1) Improvement of glycemic control. Claims 1, 2, 4, 6, 8-14, 17-29. Labeling sections 1.1, 1.2, 11, 12.1, 12.2, 14, 14.1, 14.2, 17.3

(2) Treatment of Type II diabetes. Claims 8, 10, 11-14, 17-29. Labeling sections 1.1, 1.2, 11, 12.1, 12.2, 14, 14.1, 14.2, 17.3

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

511

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☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name S. Peter Ludwig	
Address Darby & Darby P.C. 7 World Trade Center, 250 Greenwich Street	City/State New York/NY
ZIP Code 10007	Telephone Number (212) 527-7770
FAX Number *(if available)* (212) 527-7701	E-Mail Address *(if available)* pludwig@darbylaw.com

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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,866,584	2-2-1999	11-21-2012

d. Name of Patent Owner		
The Board of Supervisors of Louisiana State University and Agricultural and Mechanical College	*Address (of Patent Owner)* Louisiana State Unversity, Office of Intellectual Property, 203 Boyd Hall	
	City/State Baton Rouge/LA	
	ZIP Code 70803	FAX Number *(if available)* (225) 615-8965
	Telephone Number (225) 615-8967	E-Mail Address *(if available)* oip@lsu.edu

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)		
☞ Not applicable.	*Address (of agent or representative named in 1.e.)*	
	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

513

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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 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)

.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)* 11-25	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.)* Improvement of glycemic control. Claims 11-25. Labeling sections 1.1, 1.2, 11, 12.1, 12.2, 14, 14.1, 14.2, 17.3

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

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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 04/04/2008

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.

☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name S. Peter Ludwig	
Address Darby & Darby P.C. 7 World Trade Center, 250 Greenwich Street	City/State New York/NY
ZIP Code 10007	Telephone Number (212) 527-7770
FAX Number *(if available)* (212) 527-7701	E-Mail Address *(if available)* pludwig@darbylaw.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.

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Department of Health and Human Services
Food and Drug Administration

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

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/10
See OMB Statement on Page 3.

NDA NUMBER
20-866

NAME OF APPLICANT/NDA HOLDER
VeroScience LLC

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)
CYCLOSET

ACTIVE INGREDIENT(S)	STRENGTH(S)
bromocriptine mesylate	0.8 mg

DOSAGE FORM
Tablet

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	b. Issue Date of Patent	c. Expiration Date of Patent
5,756,513	5-26-1998	11-21-2012

d. Name of Patent Owner		
The Board of Supervisors of Louisiana State University and Agricultural and Mechanical College	Address *(of Patent Owner)* Louisiana State University, Office of Intellectual Property, 203 Boyd Hall	
	City/State Baton Rouge/LA	
	ZIP Code 70803	FAX Number *(if available)* (225) 615-8965
	Telephone Number (225) 615-8967	E-Mail Address *(if available)* oip@lsu.edu

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)		
☞ Not applicable.	Address *(of agent or representative named in 1.e.)*	
	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

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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, 3-20	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.)* (1) Improvement of glycemic control. Claims 1, 3-20. Labeling sections 1.1, 1.2, 11, 12.1, 12.2, 14, 14.1, 14.2, 17.3 (2) Treatment of Type II diabetes. Claims 11, 15 and 20. Labeling sections 1.1, 1.2, 11, 12.1, 12.2, 14, 14.1, 14.2, 17.3

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 04/04/2008

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.

☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name S. Peter Ludwig	
Address Darby & Darby PC. 7 World Trade Center, 250 Greenwich Street	City/State New York/NY
ZIP Code 10007	Telephone Number (212) 527-7770
FAX Number *(if available)* (212) 527-7701	E-Mail Address *(if available)* pludwig@darbylaw.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 # 20-866 SUPPL # HFD # 510

Trade Name Cycloset

Generic Name bromocriptine mesylate

Applicant Name VeroScience

Approval Date, If Known February 2009

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?

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#	77226	Bromocriptine mesylate 5 mg capsules
NDA#	17-962	Bromocriptine mesylate 2.5 mg tablets
NDA#	77646	Bromocriptine mesylate 2.5 mg tablets

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:

165-AD-04-03-US-1

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"):

165-AD-04-03-US-1

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 # 34,661	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: Jena M. Weber
Title: PM
Date: 2/2//2009

Name of Office/Division Director signing form: Mary Parks, M.D.
Title: Division Director, DMEP

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/

Mary Parks
2/2/2009 02:30:28 PM

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

NDA/BLA#: 20-866 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DMEP PDUFA Goal Date: 10/15/08 Stamp Date: 4/13/2008

Proprietary Name: Cycloset

Established/Generic Name: bromocriptine mesylate

Dosage Form: Tablets

Applicant/Sponsor: VeroScience

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) None
(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): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: As an adjunct to diet & exercise to improve glycemic control in patients with type 2 diabetes mellitus.

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

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the 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#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☒	Other	0 yr. __ mo.	9 yr. __ mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ 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.

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.*)

∆ 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 †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☒	Other	10 yr. __ mo.	16 yr. __ mo.	☒	☒	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	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: _____

† 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?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	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 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?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	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.

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.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

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

Q2: 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#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ 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.

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.*)

∆ 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 Section 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 some or all 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 †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	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: _____

† 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?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	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 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?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	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.

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 copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

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Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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

/s/

Jena Weber
5/1/2009 01:42:04 PM

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

NDA 20-866

Stamp Date: April 15, 2008 **PDUFA Goal Date: October 15, 2008**

HFD-510 **Trade and generic names/dosage form: Cycloset (bromocriptine mesylate) Tablets 0.8 mg**

Applicant: VeroScience **Therapeutic Class: 3**

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? * Yes.

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) *previously approved* (please complete this section for supplements only): N/A

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application: 1

Indication CYCLOSET is indicated as an adjunct to diet and exercise to improve glycemic control (hyperglycemia) in patients with type 2 diabetes mellitus.

Is this an orphan indication? NO

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

No: Please check all that apply: __X__Partial Waiver __X__Deferred ____Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____ b(4)
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- X **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____ b(4)

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): To be determined after CLN & STT reviews are completed.

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

This page was completed by:

{See appended electronic signature page}
Jena M. Weber
Regulatory Project Manager

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

/s/

Jena Weber
11/10/2008 11:44:59 AM

VeroScience, LLC

1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

VeroScience LLC certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Anthony H. Cincotta

Anthony H. Cincotta, Ph. D.
President

April 13, 2008
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☑ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Anthony H. Cincotta, PhD	President
FIRM/ORGANIZATION VeroScience LLC	
SIGNATURE Anthony H. Cincotta	DATE 04/13/2008

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Investigator	Site Address
Thomas Wade, Jr., MD	Columbus Clinic 610 19th Street Columbus, GA 31901
Sherwyn Schwartz, MD	DGD Research, Inc. 5107 Medical Drive San Antonio, TX 78229
Nizar Daboul, MD	Clinical Research Source, Inc. 5757 Monclova Road Suite 26 Maumee, OH 43537
Pamela Dugano-Daphnis, MD, MPH	347 East Parkwood Drive Friendswood, TX 77546
Lauro Lapuz, MD	Lovelace Scientific Resources, Inc. 1037 Whitney Ranch Drive Henderson, NV 89014
Todd Winter, MD	Medford Medical Clinic, Inc. 555 Black Oak Drive Suite 310 Medford, OR 97504
Mark Riederman, MD	1800 Hollister Drive Suite 211 Libertyville, IL 60048
Tushar Patel, MD	Fall River Walk-In Emergency Medical Office PC 427 Plymouth Avenue Fall River, MA 02721
Lenin Peters, MD, MRCP	Bethany Medical Center 507 Lindsay Street High Point, NC 27262
Alan Reichman, MD	Reichman and Associates 8303 Southwest Freeway Suite 580 Houston, TX 77074
Adam Karns, MD	Lovelace Scientific Resources, Inc. 8920 Wilshire Boulevard Suite 330 Beverly Hills, CA 90211
Joseph Moran, MD	Carolina Pharmaceutical Research 138 Sherlock Drive Statesville, NC 28625
Robert Schulman, MD	2441 Ridgecrest Drive Southeast Albuquerque, NM 87108
Louis Chaykin, MD	Medical Research Unlimited 21110 Biscayne Boulevard Suite 205

	Aventura, FL 33180
John Milas, MD	Internal Medicine of Greer 554-B Memorial Drive Extension Greer, SC 29651
David Morin, RPh, MD, FACP	TriCities Medical Research 1958 West State Street Bristol, TN 37620
Sanford Plevin, MD	Suncoast Clinical Research 5340 Gulf Drive Suite 203 New Port Richey, FL 34652
Ronald Surowitz, DO	Health Awareness, Inc. 210 Jupiter Lakes Boulevard Building 4000 Jupiter, FL 33458
Thomas Littlejohn III, MD	Piedmont Medical Research Associates 1901 South Hawthorne Road Suite 306 Winston-Salem, NC 27103
Cesar Albarracin, MD	Alpha Therapy Center 4626 Weber Road Suite 100 Corpus Christi, TX 78411
Samir Arora, MD	Optimed Research 8100 Ravines Edge Court Suite 240 Columbus, OH 43235
Gopalakrishna Gollapudi, MD, MPH	Diabetes Center of the Southwest 10 Desta Drive Suite 190 Midland, TX 79705
Yezid Mora, MD	Juno Research LLC 10101 Harwin Drive Suite 300 Houston, TX 77036
Jon Peterson, MD	Mercury Pharma Services, Inc. 6065 Hillcroft Avenue Suite 406 Houston, TX 77081
Amin Radparvar, MD	Missouri Endocrine and Diabetes 70 Jungermann Circle Suite 401 St. Peters, MO 63376
Steven Smallow, MD	Rapid Trials

	2846 Knight Road Bensalem, PA 19020
Gonzalo Uribe-Botero, MD	Mercury Pharma Services, Inc. 6065 Hillcroft Avenue Suite 100 Houston, TX 77081
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Investigator	Site Address
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Jambur Chandrashekar MD	81-719 Dr. Carreon Drive Blvd. Suite B1 Indio CA 92201
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Pankaj Desai MD	Crossroads Research, Inc. 25 Crossroads Drive #410 Owings Mills MD 21117
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Cecil Farrington MD	Crescent Medical Research 401 Mocksville Avenue Suite 300 Salisbury NC 28144
Jerome Fischer MD	DGD Research, Inc. 803 Castroville Road Suite 140 San Antonio TX 78237
Steven Folkerth MD	Clinical Research Center of Nevada 1022 East Sahara Ave. Las Vegas NV 89104

Investigator	Site Address
Neil Fraser MD	Troy Internal Medicine 4550 Investment Drive Suite 210 Troy MI 48098
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Darrell Herrington DO	Benchmark Research San Angelo 3555 Knickerbocker Road San Angelo TX 76904
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Richard Mills MD	Palmetto Medical Research 900 Bowman Road Suite 201 Mt. Pleasant SC 29464
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David Morin MD	Tricities Medical Research 1958 W. State Street Bristol TN 37620
Julio Pagan MD	MedSouth HealthCare 1700 Woodlawn Avenue Dyersberg TN 38024

Investigator	Site Address
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Geri Poss MD	Innovative Clinical Trials 5430 Fredericksburg Road Suite 400 San Antonio TX 78229
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Patrick Rask MD	New Hope Research of Oregon 9045 SW Barbur Blvd. Suite 106 Portland OR 97219
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Jeffrey Rosen MD	Clinical Research of South Florida 275 Alhambra Circle Coral Gables FL 33134
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John Rubino MD	Triangle Medical Research Associates 3509 Haworth Drive Suite 300 Raleigh NC 27609
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Sunil Verma MD	Sunil P. Verma, M.D., MPH, Inc. 300 Tollgate Road Suite 207 Warwick RI 02886

Investigator	Site Address
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Ralph Wade DO	Advanced Clincal Research-Bountiful 425 Medical Drive Suite 207 Bountiful UT 84010
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Hermes Florez MD	Miami VAMC VAMC Miami (151) 1201 NW 16th Street Miami FL 33125
Moti Kashyap MD	Long Beach VA Healthcare System 5901 E. 7th Street (111-111I) Long Beach CA 90822
Michael Krastins MD	Albany VAMC VAMC 111L 113 Holland Ave. Albany NY 12208
John Leidy MD	Huntington WV VAMC Research Service (151) 1540 Spring Valley Dr. Huntington WV 25704
James Levenson MD	Boston VAMC Research Service (151-MAV) 150 So. Huntington Ave Boston MA02130
Samer Nakhle MD	Las Vegas VAMC Southern Nevada VA Healthcare System P.O. Box 360001 North Las Vegas NV 89036

Investigator	Site Address
Sylvette Nazario MD	San Juan VAMC Research Service 151 10 Casia St. San Juan PR 00921-3201
Amy O'Donnell MD	Buffalo VAMC 3495 Bailey Ave. Research Service (151) Buffalo NY14215
Suzanne Quinn MD	Gainesville VAMC 1601 SW Archer Rd (111) Gainesville FL 32608
Lynnetta Skoretz MD	Loma Linda VA HCS Clinical Research Center (151-ORC) 11201 Benton Street, Room 4D-19 Loma Linda CA 92357
Udho Thadani MD	Oklahoma City VAMC 920 Stanton L. Young Blvd. WP3120 Oklahoma City OK 73104
Theordor Theodoropoulos MD	Bay Pines VAMC 10000 Bay Pines Blvd. Bldg. 100, 4D-136 Bay Pines FL 33744
Thomas Wiegmann MD	Kansas City VAMC 4801 E. Linwood Blvd. Research Service 151 Kansas City MO 64128

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009

TO BE COMPLETED BY APPLICANT

The following information concerning _____ (Name of clinical investigator), who participated as a clinical investigator in the submitted study Cycloset Safety Trial - Study No. 165-AD-04-03-US-1 (Name of clinical study) is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

b(6)

Please mark the applicable check boxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☑ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Anthony H. Cincotta, PhD	President
FIRM/ORGANIZATION VeroScience LLC	
SIGNATURE Anthony H. Cincotta	DATE 04/13/2008

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

VeroScience, LLC

1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

April 13, 2008

RE:
DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

was a site Investigator for the Cycloset Safety Trial (Study No. 165-AD-04-03-US-1) and is and would be compensated for such services. b(6)

Neither he nor anyone else had access to unblinded study data from the Cycloset Safety Trial before they were analyzed in accordance with the pre-specified Statistical Analysis Plan for the study. All study data were held in blinded fashion by the study data management organization in until several months after the final subject had exited the trial, all study queries by the sponsor were completed, and the database had been locked. No one, including the sponsor, had access to unblinded data until after the primary and secondary analyses of the Statistical Analysis Plan had been executed by b(4) b(4)

Anthony H. Cincotta, PhD

Anthony H. Cincotta

President

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
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TO BE COMPLETED BY APPLICANT

The following information concerning _____ (Name of clinical investigator), who participated as a clinical investigator in the submitted study Cycloset Safety Trial - Study No. 165-AD-04-03-US-1 (Name of clinical study) is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

b(6)

Please mark the applicable check boxes.

- [x] any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- [ ] any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- [ ] any proprietary interest in the product tested in the covered study held by the clinical investigator;
- [ ] any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Anthony H. Cincotta, PhD	President
FIRM/ORGANIZATION: VeroScience LLC	
SIGNATURE: Anthony H. Cincotta	DATE: 04/13/2008

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

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1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

April 13, 2008

RE:
DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

[redacted] was a [redacted] for the Cycloset Safety Trial (Study No. 165-AD-04-03-US-1) at the initiation of the study by its previous sponsor, PLIVA d.d. in July of 2004. The study was fully enrolled on December 31, 2005. VeroScience acquired the Cycloset NDA from PLIVA d.d. on May 16, of 2006. [redacted] became a [redacted] of the sponsor, VeroScience on [redacted] of [redacted] Consequently, [redacted] as of [redacted] b(6) b(6)

Neither he nor anyone else had access to unblinded study data from the Cycloset Safety Trial before they were analyzed in accordance with the pre-specified Statistical Analysis Plan for the study. All study data were held in blinded fashion by the study data management organization in [redacted] until several months after the final subject had exited the trial, all study queries by the sponsor were completed, and the database had been locked. No one, including the sponsor, had access to unblinded data until after the primary and secondary analyses of the Statistical Analysis Plan had been executed by [redacted] b(4) b(4)

Anthony H. Cincotta, PhD

Anthony H. Cincotta

President

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION		
NDA # 20-866		
Proprietary Name: Cycloset Established/Proper Name: bromocriptine mesylate Dosage Form: Tablets		Applicant: VeroScience
RPM: Jena Weber, 301-796-1306		Division: DMEP
NDAs: NDA Application Type: 505(b)(1) (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.)	505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **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.** ☐ No changes ☐ Updated Date of check: **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.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**	
❖ User Fee Goal Date Action Goal Date (if different)		October 15, 2008 May 5, 2009
❖ Actions		
• Proposed action		AP
• Previous actions *(specify type and date for each action taken)*		NA 11/20/98, AE 10/15/99
❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____		N/A

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[2] Characteristics	
Review priority: Standard ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC Comments: _____	
Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	1/28/09
BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	N/A
BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	N/A
Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	No
• Press Office notified of action (by OEP)	Yes
• Indicate what types (if any) of information dissemination are anticipated	X HHS Press Release FDA Talk Paper CDER Q&As Other

[2] 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	
• Is approval of this application blocked by any type of exclusivity?	No
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *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.*	No
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	N/A
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	N/A
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	N/A
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(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.)*	No
❖ Patent Information (NDAs only)	
• 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.	Verified
• 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.	N/A
• [505(b)(2) applications] If the application includes a **paragraph III 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).	N/A No paragraph III certification
• [505(b)(2) applications] For **each paragraph IV 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). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).*	N/A (no paragraph IV certification)

• [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.	N/A
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? (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))).	☐ Yes ☐ No
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? (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))).	☐ Yes ☐ No
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).*	

(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? (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). *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). *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.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	✔
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	Included
Documentation of consent/non-consent by officers/employees	Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	AP 5/05/09 AE 10/15/99 NA 11/20/98
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	4/29/09
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	5/1/09 (PI, PCI) 12/26/08 (carton/container)
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	Patient Counseling Insert
• 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)	5/1/09

[3] Fill in blanks with dates of reviews, letters, etc.

• Original applicant-proposed labeling	✓
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ 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	12/26/08
❖ Labeling reviews *(indicate dates of reviews and meetings)*	✓ RPM ✓ DMEDP ✓ DRISK ✓ DDMAC
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	9/26/08, 12/18/08, and 4/07/09
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	Filing Review: 1/29/09 Memo of Filing Meeting: 6/4/08 (attached to Filing Rev)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	2/2/09
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant in on the AIP	No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	No N/A N/A
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	1/30/09
❖ 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)*	Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	None
• Outgoing communications *(if located elsewhere in package, state where located)*	
• Incoming submissions/communications	
❖ Postmarketing Commitment (PMC) Studies	None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	Peds Studies (3)
• Incoming submission documenting commitment	
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	Included
❖ Internal memoranda, telecons, etc.	Included

[4] Filing reviews for other disciplines should be filed behind the discipline tab.

❖ Minutes of Meetings	Included
• PeRC *(indicate date; approvals only)*	1/28/09
• Pre-Approval Safety Conference *(indicate date; approvals only)*	Not applicable
• Regulatory Briefing *(indicate date)*	No mtg
• Pre-NDA/BLA meeting *(indicate date)*	No mtg
• EOP2 meeting *(indicate date)*	No mtg
• Other (e.g., EOP2a, CMC pilot programs)	None
❖ Advisory Committee Meeting(s)	No AC meeting
• Date(s) of Meeting(s)	None
• 48-hour alert or minutes, if available	None
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	None
Division Director Summary Review *(indicate date for each review)*	5/05/09
Cross-Discipline Team Leader Review *(indicate date for each review)*	None
Clinical Information	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	3/25/09
• Clinical review(s) *(indicate date for each review)*	1/16/09
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	N/A
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	1/16/09 (MOR)
❖ 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	1/16/09
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	12/1/08 (CBER, Bruce Schneider, M.D.).
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	NN
❖ Risk Management • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* • REMS Memo *(indicate date)* • REMS Document and Supporting Statement *(indicate date(s) of submission(s))*	None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	11/19, 1/12/09
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	N/A
Clinical Microbiology Review(s) *(indicate date for each review)*	N/A

[5] Filing reviews should be filed with the discipline reviews.

Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	None
Statistical Team Leader Review(s) *(indicate date for each review)*	11/18/08
Statistical Review(s) *(indicate date for each review)*	11/18/08
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	10/8/08
Clinical Pharmacology review(s) *(indicate date for each review)*	10/8/08
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	10/15/08
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	None
• Supervisory Review(s) *(indicate date for each review)*	10/14/08
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	10/14/08
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	None
❖ ECAC/CAC report/memo of meeting	None
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	None requested
CMC/Quality ☐ None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	10/31/08
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	10/6/08
• CMC/product quality review(s) *(indicate date for each review)*	10/6/08
• BLAs only: Facility information review(s) *(indicate dates)*	None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)*	N/A
• BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	N/A
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	10/6/08
☐ Review & FONSI *(indicate date of review)*	

☐ Review & Environmental Impact Statement *(indicate date of each review)*	10/6/08
❖ NDAs: Methods Validation	Completed
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: May 2008 Acceptable
• BLAs: o TBP-EER o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	N/A

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

/s/

Jena Weber
5/5/2009 01:23:33 PM

VeroScience, LLC
1334 Main Road, Tiverton, RI 02878
(p) 401 816 0525, (fax) 401 816 0524

May 1, 2009

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Cycloset Label Revision and FDA Information Request Letter of 05/01/09
Amendment 49

Dear Dr. Parks,

Reference is made to an information request letter (herewith attached) received from FDA on May 1, 2009 requesting VeroScience to conduct two clinical trials with Cycloset in subjects with type 2 diabetes to determine its efficacy in improving glycemic control in these studies as follows:

1) A 6-month, double-blind, controlled clinical trial evaluating Cycloset as add-on to Thiazolidinedione therapy.
2) A 6-month, double-blind, controlled clinical trial evaluating Cycloset as add-on to insulin therapy.

Reference is also made to the latest FDA revision to the Cycloset package insert that was received via email from our project manager, Jena Weber on April 27, 2009 (herewith attached).

Reference is also made to a phone call request from Jena Weber on May 1, 2009 to delineate the timelines for the Pediatric Studies Plan for Cycloset in the Treatment of Type 2 Diabetes.

We acknowledge FDA's request to study Cycloset as add-on to thiazolidinediones and also as add-on to insulin in patients with type 2 diabetes and we intend to pursue the design and conduct of such studies. This submission contains the protocol synopses for each of the above mentioned Cycloset efficacy trials, including dates of study initiation, study completion and study report submission to FDA. This submission also contains our latest version of the Cycloset package insert that incorporates all of the latest FDA revisions to it. Finally, we also include in this submission, an updated table of the timelines for the conduct of the pediatric studies for Cycloset treatment of type 2 diabetes previously submitted to FDA in amendment 42 (December 2008).

FDA Form 356h and the above referenced emails follow this letter. We are providing an original (blue) archival copy, a (tan) clinical copy and three (black) desk copies of this submission. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta, PhD
President and Chief Scientific Officer

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-866

INFORMATION REQUEST LETTER

5/1/09

VeroScience, LLC
Attention: Anthony Cincotta, Ph.D.
President and CSO
1334 Main Road
Tiverton, RI 02878

Dear Dr. Cincotta:

Please refer to your August 22, 1997, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cycloset (bromocriptine mesylate) 0.8 mg tablets.

We also refer to your submission dated April 13, 2008, which constituted a complete response to our October 15, 1999, action letter.

We have the following comments and information requests.

A considerable subset of patients with type 2 diabetes mellitus use a thiazolidinedione or insulin for glycemic control. As previously communicated, there is limited information supporting the efficacy of Cycloset in these settings based on the data submitted to date. Therefore, we strongly encourage you to conduct the following two clinical trials in the near future:

1. A 6-month, double-blind, controlled clinical trial evaluating Cycloset as add-on to thiazolidinedione therapy.

2. A 6-month, double-blind, controlled clinical trial evaluating Cycloset as add-on to insulin therapy.

Please respond to this letter in writing. Include your rationale if you are not planning to conduct such trials.

If you are planning to conduct such trials, include in your response the anticipated timeframe for initiating these trials. You may include a set of questions at the time of protocol submission if there are specific aspects of the protocols for which you are seeking input from the Division.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
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/

Mary Parks
5/1/2009 08:28:42 AM

VeroScience, LLC

1334 Main Road, Tiverton, RI 02878
(p) 401 816 0525, (fax) 401 816 0524

April 13, 2009

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Cycloset Label Revision – Accepted FDA revisions
Amendment 48

Dear Dr. Parks,

Reference is made to an email (herewith attached) received from our FDA project manager, Jena Weber, on April 8, 2009 requesting our revision of the Cycloset label per FDA recommendations attached thereto. We have accepted and incorporated all the FDA recommendations to the label and this submission contains our latest such version of the Cycloset label and our responses to certain FDA comments made on the last version of the Cycloset label.

We acknowledge FDA's request in the latest Cycloset label revision for postmarketing commitments to study Cycloset as add-on to thiazolidinediones and also as add-on to insulin in patients with type 2 diabetes and we intend to pursue the design and conduct of such studies.

FDA Form 356h and the above referenced email from Jena Weber follow this letter. We are providing an original (blue) archival copy, a (tan) clinical copy and three (black) desk copies of this submission. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta, PhD
President and Chief Scientific Officer

VeroScience, LLC

1334 Main Road, Tiverton, RI 02878
(p) 401 816 0525, (fax) 401 816 0524

April 13, 2009

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Cycloset Label Revision – Accepted FDA revisions
Amendment 48

Dear Dr. Parks,

Reference is made to an email (herewith attached) received from our FDA project manager, Jena Weber, on April 8, 2009 requesting our revision of the Cycloset label per FDA recommendations attached thereto. We have accepted and incorporated all the FDA recommendations to the label and this submission contains our latest such version of the Cycloset label and our responses to certain FDA comments made on the last version of the Cycloset label.

FDA Form 356h and the above referenced emails from Dr. Misbin follow this letter. We are providing an original (blue) archival copy, a (tan) clinical copy and three (black) desk copies of this submission. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta, PhD
President and Chief Scientific Officer

Weber, Jena M

From: cderdocadmin@cder.fda.gov
Sent: Tuesday, March 31, 2009 9:42 AM
: Weber, Jena M; Campbell, Cheryl; Griffis, Melina
ıbject: DFS Email - N 020866 N 000 AZ 13-Apr-2008 - Forms

Attachments: 0900146980324542.drl; 0900146980324542.pdf

0900146980324542 .drl (169 B) 0900146980324542 .pdf (20 KB)

Document room update the following:

	Decision Date	Decision Code
N 020866 N 000 AZ 13-Apr-2008	31-Mar-2009	:

Document Type: Forms
Form Group: CONSULT
Form Name: OSE Consult Request
Submission Description: Tradename Request #4

Author(s)/Discipline(s)

1. Jena Weber, CSO

.gner(s)

1. Jena Weber
Please re-evaluate ASAP. Last DMEPA review found tradename acceptable (12/19/08). 90-day AC period has expired.
31-Mar-2009

Supervisory Signer(s)

1. Jena Weber
Please re-evaluate ASAP. Last DMEPA review found tradename acceptable (12/19/08). 90-day AC period has expired.
31-Mar-2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
OSE
.t. Cheryl Campbell

FROM: DMEP
Jena Weber, PM

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
3/30/09		20-866	Tradename Proposal	4/13/08

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Bromocriptine mesylate	S	Anti-diabetic	4/10/09

NAME OF FIRM: VeroScience, LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY REVIEW
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER (SPECIFY BELOW):
OTHER (SPECIFY BELOW):	

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **Approvable letter for this NDA issued on 10/15/1999;. tradename "Cycloset," was acceptable. Also reference your review from December 18, 2008, (OSE-RCM 2008-1940); tradename found acceptable. Please re-evaluate as 90-day period has expired. DMEP plans to take an action (AP) by April 15th, 2009. All labeling is available via EDR.**

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
Jena Weber, 301-796-1306	☒ DFS ONLY X HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Jena Weber
3/31/2009 09:41:26 AM
Please re-evaluate ASAP. Last DMEPA review found tradename acceptable (12/19/08). 90-day AC period has expired.

DMETS EXPERT PANEL
PROPRIETARY NAME EVALUATION

Proposed PROPRIETARY Name: **Cycloset**

Proposed ESTABLISHED Name: bromocriptine mesylate

USAN Stem?

Sound-alike/Look-alike Names of CONCERN ONLY (See worksheet on page 2):

Name	*Available Strength(s)/Dosage Form(s)*	*Level of LA Concern* 1=High 2=Moderate 3=Low	*Level of SA Concern* 1=High 2=Moderate 3=Low

DDMAC RECOMMENDATION: X **Acceptable** Unacceptable

Comments/Concerns:

Sauers 03.19.09

SIGNATURE OF DDMAC REPRESENTATIVE DATE

SAFETY EVALUATOR RECOMMENDATION: ~ Unacceptable ~ Acceptable

Comments/Concerns:

Weber, Jena M

From: Aljuburi, Lina
Sent: Tuesday, March 17, 2009 3:38 PM
To: Parks, Mary H; Joffe, Hylton
Cc: Weber, Jena M
Subject: FW: Cycloset/NDA 20-866

Attachments: Cycloset NC.doc

We've got clearance from DMEPA for the Cycloset name for another 90 days!

Thanks,
Lina

From: Wright, Mildred
Sent: Tuesday, March 17, 2009 3:18 PM
To: Aljuburi, Lina; Weber, Jena M
Subject: Cycloset/NDA 20-866

Lina/Jena,
Name good to go.
Millie

Cycloset NC.doc
(40 KB)

VeroScience, LLC
1334 Main Road, Tiverton, RI 02878
(p) 401 816 0525, (fax) 401 816 0524

March 10, 2009

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

RECEIVED
MAR 13 2009
CDER CDR
DUPLICATE
N-000-BM
ORIG AMENDMENT

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Submission of previously emailed information for Cycloset Safety Trial
Amendment 47

Dear Dr. Parks,

Reference is made to several emails (herewith attached) received from our FDA medical reviewer of the Cycloset NDA, Dr. Robert Misbin, requesting additional information and analyses from the Cycloset Safety Trial (Study number 165-AD-04-03-US-1) database. We have previously responded to these requests via email to Dr. Misbin and are now also officially submitting these responses to the Cycloset NDA 20-866 in this submission. This submission contains:

1. January 5, 2009 email to Dr. Misbin with attachment of analyses of table of baseline concomitant diabetes and cardiovascular medications among subjects with a CVD SAE in the Cycloset Safety Trial (Study No. 165-AD-04-03-US-1)
2. January 8, 2009 email to Dr. Misbin with attachment of summary write-up on the baseline diabetes and cardio-protective medications at baseline among subjects in the Cycloset Safety Trial.
3. January 9, 2009 email to Dr. Misbin with attachment of information regarding relation between baseline history of stoke or coronary revascularization surgery and CVD event occurrence in the Cycloset Safety Trial.
4. January 20, 2009 email to Dr. Misbin with attachment of information regarding subjects experiencing an adverse event of hypotension or orthostatic hypotension during the Cycloset Safety Trial.
5. March 4, 2009 email to Dr. Misbin with attachment of information on an analysis of the relation between cardio-protective medications at baseline among subjects in the Cycloset Safety Trial and between group differences in the percent of subjects having a CVD endpoint event.
6. A summary table from the above submissions on at baseline and from baseline concomitant diabetes and cardiovascular medications among subjects in the Cycloset Safety Trial.

FDA Form 356h and the above referenced emails from Dr. Misbin follow this letter. We are providing an original (blue) archival copy, a (tan) clinical copy and three (black) desk copies of this submission. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta

Anthony H. Cincotta, PhD
President and Chief Scientific Officer

Weber, Jena M

From: Aljuburi, Lina
Sent: Tuesday, March 10, 2009 4:47 PM
Weber, Jena M
Subject: FW: Trade name review for NDA 20-866 Cycloset

FYI

From: Wright, Mildred
Sent: Tuesday, March 10, 2009 4:45 PM
To: Aljuburi, Lina
Cc: Campbell, Cheryl; Wright, Mildred
Subject: RE: Trade name review for NDA 20-866 Cycloset

We will re-open . Won't need a new consult.
Millie

From: Aljuburi, Lina
Sent: Tuesday, March 10, 2009 1:54 PM
To: Wright, Mildred
Cc: Campbell, Cheryl; Weber, Jena M
Subject: Trade name review for NDA 20-866 Cycloset

Hi Millie,

We have the following application:

NDA 20-866
Trade name: Cycloset
Generic name: bromocriptine

DMEPA completed a review on December 18, 2008 (signed off 12/19/08), stating the trade name "Cycloset" is acceptable. We have yet to take an action (for oh so many reasons ;) and realize that we will not be making the cut-off of 90-days prior to the trade name being found acceptable. So we need DMEPA to do the abbreviated review they do in these cases.

The OSE RCM # is 2008-1940

Melina Griffis' review is attached here for your reference.

<< File: Cycloset_TradeNameReview.pdf >>
Do you need another consult - or can you reopen the old one?

Feel free to contact me for whatever additional information you need to complete this request.

Many thanks,
Lina

Lina Aljuburi, Pharm.D., M.S.
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
l.aljuburi@fda.hhs.gov
301-796-1168 (phone)
301-796-9712 (fax)

VeroScience, LLC

1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

March 3, 2009

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

RECEIVED
MAR 04 2009
CDER CDR

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Response to Cycloset PI and PPI revisions
Amendment 46

Dear Dr. Parks,

Reference is made to an email (herewith attached) received from our FDA project manager, Jena Weber, on February 20, 2009 containing the FDA's most current revisions to the Cycloset Package Insert (PI) and Patient Package Insert (PPI). We have reviewed these revisions and accepted the vast majority of the FDA suggested changes to the Cycloset PI and PPI. This submission includes a) our updated version of the Cycloset PI and PPI taking these latest FDA recommendations into account and b) our responses to FDA's comments and queries regarding the PI (this document addresses the rationale for those particular instances in the current label revision where we either provided additional text other than that suggested by the Agency or provided responses to questions raised in the comments posted in the label by the Agency that were not fully self explanatory in the revised label itself).

FDA Form 356h and the above referenced email from Jena Weber follow this letter. We are providing an original (blue) archival copy, a (tan) clinical copy and three (black) desk copies as well as a CD that contains the entire contents of this submission. This CD was scanned by Symantec Antivirus Program 10.1.0.394 Scan engine 81.3.0.13 Virus Definition File 3/2/2009 rev.2 and found to be virus-free. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta

Anthony H. Cincotta, PhD
President and Chief Scientific Officer

Weber, Jena M

From: Joffe, Hylton
Sent: Thursday, February 26, 2009 3:35 PM
To: Parks, Mary H; Weber, Jena M
Subject: RE: Cycloset NDA 20-866

Thanks - so the only outstanding issues are my memo and labeling. After I finish the AC stuff I'll wrap up my memo.

Hylton

From: Parks, Mary H
Sent: Thursday, February 26, 2009 3:19 PM
To: Weber, Jena M; Joffe, Hylton
Subject: FW: Cycloset NDA 20-866

Okay. We can take an action.

From: Ripper, Leah W
Sent: Thursday, February 26, 2009 2:29 PM
To: Parks, Mary H; Galliers, Enid M; Aljuburi, Lina
Subject: RE: Cycloset NDA 20-866

Yep, happens all the time, especially when pending NAI. Of course, there might be times when it's not NAI (or minor stuff) and you would want ot discuss the findings with DSI . . . . .

Lee

From: Parks, Mary H
Sent: Thursday, February 26, 2009 8:18 AM
To: Galliers, Enid M; Aljuburi, Lina; Ripper, Leah W
Subject: FW: Cycloset NDA 20-866

Can you advise me here? Can we take an action for Cycloset with just the inspection summary signed off in DFS and a "pending - interim NAI" for one site?

Thanks.

From: Weber, Jena M
Sent: Wednesday, February 25, 2009 3:38 PM
To: Parks, Mary H; Joffe, Hylton
Subject: RE: Cycloset NDA 20-866

Mary,

Roy called me this afternoon to discuss the outstanding clinical inspection regarding Dr. Barengolts. Bottom line is that DSI does not know when they may have the individual report finalized. Roy said that this has never been a problem before with our Division or other review divisions. He referred me to the inspection summary signed off in DFS (by Roy and his team leader) on January 12, 2009. The final inspection classification states "pending - interim NAI," for Dr. Barengolts; the 2 other reports on Drs. Littlejohn and Fisher were designated "VAI." Let me know how you would like to proceed; we can phone Roy tomorrow if you like.

Thanks,
Jena

From: Parks, Mary H
Sent: Monday, February 23, 2009 9:08 PM
To: Joffe, Hylton
Cc: Weber, Jena M
Subject: RE: Cycloset NDA 20-866

They need to finalize their report in DFS.

From: Joffe, Hylton
Sent: Monday, February 23, 2009 7:44 PM
To: Parks, Mary H
Cc: Weber, Jena M
Subject: FW: Cycloset NDA 20-866

FYI, Mary — we've been trying to get this written DSI report for weeks, if not months, but it hasn't happened yet.

DSI said that the inspection was acceptable even though it hasn't officially been written up. Do we need an official report or is an email saying that it is acceptable good enough? I thought we needed all reviews in DFS before we can take an action but wasn't sure if we've been applying that rule to something like this.

Hylton

From: Weber, Jena M
Sent: Monday, February 23, 2009 2:29 PM
To: Joffe, Hylton
Subject: FW: Cycloset NDA 20-866

FYI, See below.
Jena

From: Blay, Roy A
Sent: Monday, February 23, 2009 2:25 PM
To: Weber, Jena M
Subject: RE: Cycloset NDA 20-866

Jena,

Thanks for the reminder. My understanding is that it has been sent to me, but I don't have it yet. Please let me know if this will be a problem for you with taking an action.

Roy

From: Weber, Jena M
Sent: Monday, February 23, 2009 12:50 PM
To: Blay, Roy A
Cc: Joffe, Hylton
Subject: Cycloset NDA 20-866

Roy,

Just checking in to see if a final written report was issued on Eleana Barengolts, M.D. We are getting very close to taking an action on this submission.

thanks,
Jena

Project Manager
Division of Metabolism & Endocrinology Products
Jena.Weber@fda.hhs.gov
301-796-1306

VeroScience, LLC

1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

February 16, 2009

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

RECEIVED
FEB 17 2009
CDR

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Response to FDA DMEP Questions
Amendment 45

Dear Dr. Parks,

Reference is made to an email (herewith attached) received from our FDA project manager, Jena Weber, on February 9, 2009 requesting responses to questions posed by Dr. Hylton Joffe regarding data from the Cycloset Safety Trial (Study No. 165-AD-04-03-US-1). This submission provides the requested responses to those questions.

FDA Form 356h and the above referenced email from Jena Weber follow this letter. We are providing an original (blue) archival copy, a (tan) clinical copy and three (black) desk copies. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta

Anthony H. Cincotta, PhD
President and Chief Scientific Officer

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
DDMAC
Att. Sam Skariah

FROM: DMEP
Jena Weber, PM

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/30/09		20-866	PI/PPI	1/21/09

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Bromocriptine mesylate	S	Anti-diabetic	**2/9/09**

NAME OF FIRM: VeroScience, LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: PP/PPI

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- ☐ TYPE A OR B NDA REVIEW
- ☐ END OF PHASE II MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **This is the current label submitted by VeroSceince for Cycloset. It includes our first round suggested revisions. Please review and comment as appropriate. I will include you in the final labeling meeting. We plan to take an action (AP) in 7 – 10 days.**

NAME AND PHONE NUMBER OF REQUESTER
Jena Weber, 301-796-1306

METHOD OF DELIVERY (Check one)
☒ DFS ONLY X HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

19 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Jena Weber
1/30/2009 03:39:57 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 20-866 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Cycloset
Established Name: bromocriptine mesylate tablets
Strengths: 0.8 mg
Applicant: VeroScience Inc.
Agent for Applicant: N/A

Date of Application: April 13, 2008
Date of Receipt: April 15, 2008
Date clock started after UN:
Date of Filing Meeting: June 4, 2008
Filing Date: June 15, 2008
Action Goal Date (optional): User Fee Goal Date: October 15, 2008

Indication requested: CYCLOSET is indicated as an adjunct to diet and exercise to improve glycemic control (hyperglycemia) in patients with type 2 diabetes mellitus (type 2 diabetes).
CYCLOSET is indicated as:

- Monotherapy in addition to diet and exercise.
- Adjunctive therapy in patients with type 2 diabetes mellitus who are failing therapy with insulin secretagogues (e.g. sulfonylurea) or metformin alone or another oral agent to improve glycemic control.
- Combination therapy with insulin if insulin alone does not provide adequate glycemic control.

Type of Original NDA: (b)(1) X (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S
Resubmission after withdrawal? NO Resubmission after refuse to file? NO
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted: YES

User Fee Status: Paid ☐ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) X

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b).

Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? NO
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

  N/A

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? NO
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? NO

- Does the submission contain an accurate comprehensive index? NO
  If no, explain:

- Was form 356h included with an authorized signature? YES
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

  1. This application is a paper NDA NO

  2. This application is an eNDA or combined paper + eNDA YES
     This application is: All electronic ☐ Combined paper + eNDA ☐
     This application is in: NDA format X CTD format ☐
     Combined NDA and CTD formats

     Does the eNDA, follow the guidance?
     (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES

     If an eNDA, all forms and certifications must be in paper and require a signature.

     If combined paper + eNDA, which parts of the application were submitted in electronic format? All.

     Additional comments: Appropriate paper signatures obtained.

3. This application is an eCTD NDA. NO
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments: – **Noted and acknowledged.**

- Patent information submitted on form FDA 3542a? YES

- Exclusivity requested? _____ NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES

- Is this submission a partial or complete response to a pediatric Written Request? NO

  If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES

- PDUFA and Action Goal dates correct in tracking system? YES
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: **34,661**

- Are the trade, established/proper, and applicant names correct in COMIS? YES
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ NO
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? YES

- Risk Management Plan consulted to OSE/IO? YES

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? N/A

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES
  If no, did applicant submit a complete environmental assessment? YES
  If EA submitted, consulted to EA officer, OPS? YES
- Establishment Evaluation Request (EER) submitted to DMPQ? YES
- If a parenteral product, consulted to Microbiology Team? N/A

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 4, 2008

NDA 20-866

DRUG NAME: Cycloset (bromocriptine mesylate) tablets 0.8 mg

APPLICANT: VeroScience Inc.

BACKGROUND: NDA was submitted August 1997; an **approvable** letter was issued October 15, 1999. The company provided a complete response on April 13, 2008.

ATTENDEES: Drs. Joffe, Misbin, Pian, Sahlroot, Kuijpers, Choe, Vaidyanathan,Ysern, and Ms. Weber

ASSIGNED REVIEWERS (including those not present at filing meeting): Biswas, Blay, Carothers, Vishwanathan, Griffis, Lewin.

Discipline/Organization	Reviewer
Medical:	Joffe/Misbin
Secondary Medical:	NN
Statistical:	Sahlroot/Pian
Pharmacology:	Davis-Bruno/Kuijpers
Statistical Pharmacology:	NN
Chemistry:	Al-Hakim/Ysern
Environmental Assessment (if needed):	NN
Biopharmaceutical:	Choe/Vaidyanathan
Microbiology, sterility:	NN
Microbiology, clinical (for antimicrobial products only):	NN
DSI:	CLN, BPH (Blay, Vishwanathan)
OPS:	NN
Regulatory Project Management:	Aljuburi/Weber
Other Consults:	

Per reviewers, are all parts in English or English translation? YES
If no, explain:

CLINICAL FILE

- Clinical site audit(s) needed? YES
  If no, explain:
- Advisory Committee Meeting needed? _____ NO

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A

CLINICAL MICROBIOLOGY N/A

STATISTICS FILE

BIOPHARMACEUTICS FILE

- Biopharm. study site audits(s) needed? YES

PHARMACOLOGY/TOX FILE

- GLP audit needed? NO

CHEMISTRY FILE X REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES
- Sterile product? NO
  If yes, was microbiology consulted for validation of sterilization? N/A

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☐ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
Application poorly assembled, difficult to locate files, data, forms, etc.

X No filing issues have been identified.

☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. X If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

Jena M. Weber
Regulatory Project Manager

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

/s/

Jena Weber
1/29/2009 02:16:19 PM
CSO

VeroScience, LLC

1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

January 21, 2009

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Latest Revision to Cycloset Label
Amendment 44

Dear Dr. Parks,

Reference is made to an email (herewith attached) received from our FDA project manager, Jena Weber, of January 8, 2009 requesting revisions to the latest version of the Cycloset label. This submission includes 1) the VeroScience revisions to the Cycloset label a) in final format, b) with FDA accepted changes highlighted, and c) with FDA accepted changes and VeroScience changes highlighted and 2) VeroScience responses to FDA comments to the Cycloset label where such responses were required or appropriate.

FDA Form 356h and the above referenced email from Jena Weber follow this letter. We are providing an original (blue) archival copy, a (tan) clinical copy and three (black) desk copies. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta, PhD

Anthony H. Cincotta, PhD
President and Chief Scientific Officer

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE:	January 12, 2009
TO:	Jena Weber, Regulatory Project Manager Robert Misbin, M.D., Medical Officer Division of Metabolism and Endocrinology Products
FROM:	Roy Blay, Ph.D. Good Clinical Practice Branch 1 Division of Scientific Investigations
THROUGH:	Constance Lewin, M.D., M.P.H. Branch Chief Good Clinical Practice Branch 1 Division of Scientific Investigations
SUBJECT:	Evaluation of Clinical Inspections.
NDA:	20-866
APPLICANT:	VeroScience,
DRUG:	Cycloset (bromocriptine mesylate) tablets
NME:	Yes
THERAPEUTIC CLASSIFICATION:	Standard Review
INDICATION:	Treatment of Type 2 diabetics with adjunct Cycloset therapy to determine whether there is a lessening in the number of serious adverse events as compared to placebo
CONSULTATION REQUEST DATE:	August 13, 2008
DIVISION ACTION GOAL DATE:	October 1, 2008
PDUFA DATE:	October 15, 2008

I. BACKGROUND:

The conduct of protocol #165-AD-04-03-US-1, entitled "A Randomized, Double-Blind, Placebo-Controlled Trial to Assess Safety and Tolerability during Treatment of Type 2 Diabetes with Usual Diabetes Therapy and Either Cycloset® or Placebo" was inspected.

The sites of Drs. Littlejohn, Fischer, and Barengolts were selected on the basis of the enrollment of large numbers of study subjects.

The primary objective of this study was to determine whether adjunct therapy of Type 2 diabetics with Cycloset® would lessen the number of serious adverse events as compared to placebo.

II. RESULTS (by Site):

Name of CI, Location	Protocol #:/ # of Subjects/	Inspection Dates	Final Classification
Thomas Littlejohn, M.D. Piedmont Medical Research, 1901 S. Hawthorne Road, Suite 306 Winston-Salem, NC 27103	165-AD-04-03-US-1/ 152/	6-10 Oct 2008	NAI
Jerome Fischer, M.D. DGD Research Inc. 803 Castroville Road, Suite 140 San Antonio, TX 78237	165-AD-04-03-US-1/ 81/	2-14 Oct 2008	VAI
Elena Barengolts, M.D. Chicago Westside VAMC CHCS Westside 820 S. Damien Ave. M/C111 Chicago, IL 60654	165-AD-04-03-US-1/ 136/	20-24 Oct 2008	Pending. Interim classification NAI.

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Thomas Littlejohn, M.D.
   Piedmont Medical Research, 1901 S.
   Hawthorne Road, Suite 306
   Winston-Salem, NC 27103

   a. **What was inspected:** 175 subjects were screened for the study, 152 were randomized, 85 completed the study, and 67 were dropped after enrollment because of protocol violations and adverse events. The study records for 16 subjects were reviewed in-depth and compared against source documents. Consent forms were present for all subjects. Medical histories, laboratory

reports, adverse event, concomitant medication, and drug accountability reporting were reviewed.

b. **General observations/commentary**: Review of the records noted above revealed no significant discrepancies/regulatory violations.

c. **Assessment of data integrity**: Data appear acceptable in support of the respective application.

2. Jerome Fischer ✓
DGD Research Inc.
803 Castroville Road, Suite 140
San Antonio, TX 78237

a. **What was inspected**: 131 subjects were screened for the study, 81 were enrolled, 50 were screen failures, and 33 completed the study. The study records for 31 subjects were reviewed in-depth, and signed consent forms were present for all reviewed subject records. Adverse event, concomitant medication, and drug accountability reporting were reviewed. Source documents were compared with the corresponding CRFs and the data listings accompanying the assignment.

b. **General observations/commentary**: Subject 03980 was dispensed placebo in error rather than the study drug.

c. **Assessment of data integrity**: Data appear acceptable in support of the respective application; however, the review division should consider the impact, if any, of the data regarding subject 03980 receiving placebo.

3. Elena Barengolts, M.D. ✓
Chicago Westside VAMC
CHCS Westside
820 S. Damien Ave.
M/C111
Chicago, IL 60654

a. **What was inspected**: 212 subjects were screened for the study, 136 were randomized, and 76 completed the study. The study records for the 136 randomized subjects were reviewed and compared against source documents. Consent forms, medical histories, laboratory reports, glycosylated hemoglobin values (HgbA1c) levels, adverse events, concomitant medications, intercurrent illnesses, and drug accountability reporting were reviewed.

b. **General observations/commentary**: Review of the records noted above revealed no significant discrepancies/regulatory violations.

c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

Observations noted above are based on the draft inspection report received from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Receipt and review of the EIR for Dr. Barengolt's site is pending. An addendum to this clinical inspection summary will be forwarded to the review division should there be any observations of clinical and regulatory significance discovered after reviewing the EIR.

The data generated by the clinical sites of Drs. Barengolt, Littlejohn and Fischer appear acceptable in support of the respective application; however, the review division should consider the impact, if any, of the data from Dr. Fischer's site regarding subject 03980 receiving placebo.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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

/s/

Roy Blay
1/12/2009 02:15:08 PM
CSO

Constance Lewin
1/12/2009 02:29:13 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
OSE
Att. Cheryl Campbell

FROM: DMEP
Jena Weber, PM

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/9/09		20-866		12/26/08

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Bromocriptine mesylate	S	Anti-diabetic	**1/26/09**

NAME OF FIRM: VeroScience, LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- ☐ TYPE A OR B NDA REVIEW
- ☐ END OF PHASE II MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **Response to FDA labeling (from OSE) comments on carton/containers. See attachement.**

NAME AND PHONE NUMBER OF REQUESTER
Jena Weber, 301-796-1306

METHOD OF DELIVERY (Check one)
☒ DFS ONLY

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

DUPLICATE

VeroScience, LLC

1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

December 26, 2008

RECEIVED
DEC 29 2008
CDER CDR

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

N-000 (B2)

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Response to Issues and Questions for Cycloset Label
Amendment 41

Dear Dr. Parks,

Reference is made to several emails (herewith attached) received from FDA during the past few weeks requesting more information on the Cycloset NDA 20-866. Firstly, we received emails from Dr. Robert Misbin of DMEP of December 15 and 16, 2008 requesting information on a) certain psychiatric disorders adverse events for all subjects and b) a narrative of an adverse event – pulmonary fibrosis for a single subject occurring during the Cycloset Safety Trial (study no. 165-AD-04-03-US-1). Secondly, we received other emails from our FDA project manager, Jena Weber, of December 17 and 23, 2008 requesting a) changes to the Cycloset container and carton labels requested by OSE and b) information regarding 1) the Cycloset Pediatric Study Plan and 2) certain analyses of cardiovascular serious adverse events in the Cycloset Safety Trial. This submission provides responses to all those email requests. This submission contains 1) the requested data on psychiatric disorders in the Cycloset Safety Trial submitted via email to Dr. Misbin on December 17, 2008, 2) The requested changes to the Cycloset Pediatric Study Plan, 3) The requested data on baseline concomitant diabetes and cardiovascular disease medications as well as history of ischemic heart disease among subjects in the Cycloset Safety Trial and 4) the requested changes to the container and carton labels for Cycloset by OSE.

FDA Form 356h and the above referenced emails from Jena Weber and Dr. Misbin follow this letter. We are providing an original (blue) archival copy, a clinical (tan) copy, and three (black) desk copies of this submission. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta

Anthony H. Cincotta, PhD
President and Chief Scientific Officer

Section 4

Changes to Cycloset Container and Carton Labels

Changes to Cycloset Container and Carton Labels

as Requested by OSE via Email of December 17, 2008

(attached hereto)

6 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

From: Weber, Jena M [mailto:jena.weber@fda.hhs.gov]
Sent: Wednesday, December 17, 2008 9:35 AM
To: Anthony Cincotta
Subject: See attached
Importance: High

Anthony,

Here are the comments that I received from OSE; please address these.

Thanks,
Jena

<<OSE Labeling comments.doc>>

Project Manager
Division of Metabolism & Endocrinology Products
Jena.Weber@fda.hhs.gov
301-796-1306

OSE Labeling comments, please address.

We continue to have concerns with the size of the company name and logo on the container labels. As currently displayed the size of the company name and logo, "Veroscience", is of similar size and prominence compared to the proprietary name and strength and should be decreased so that it does not compete with the proprietary and established names and strength. Revise so that the company name and logo is relocated to the bottom of the principle display panel which is a less prominent area.

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

/s/

Jena Weber
1/9/2009 09:47:55 AM

VeroScience, LLC
1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

January 5, 2009

RECEIVED
JAN 06 2009
CDR

ORIG AMENDMENT

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Electronic Copy of Amendment 27 - Cycloset Safety Trial Clinical Study Report
Amendment 43

Dear Dr. Parks,

Reference is made to an email (herewith attached) received from our FDA project manager, Jena W eber, of January 5, 2009 requesting an electronic copy of Sections 14 and 16 of the Cycloset Safety Trial Clinical Study Report - Amendment 27 to the Cycloset NDA 20-866. This submission provides an electronic copy of the entire Cycloset Safety Trial Clinical Study Report (Amendment 27 to the Cycloset NDA) inasmuch as Sections 14 and 16 comprise the majority of the Report. A paper copy of the Table of Contents for the Volumes of Amendment 27 as well as for Sections 14 and 16 thereof are included for assistance in reviewing the Amendment.

FDA Form 356h and the above referenced email from Jena Weber follow this letter. We are providing an original (blue) archival copy containing the CD with the Amendment 27. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta

Anthony H. Cincotta, PhD
President and Chief Scientific Officer

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
OSE
Att. Cheryl Campbell

FROM: DMEP
Jena Weber, PM

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
12/5/08		20-866	Tradename Proposal	4/13/08

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Bromocriptine mesylate	S	Anti-diabetic	**12/29/08**

NAME OF FIRM: VeroScience, LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- ☐ TYPE A OR B NDA REVIEW
- ☐ END OF PHASE II MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **Approvable letter for this NDA issued on 10/15/1999.** At this time, the tradename "Cycloset," was acceptable. Please evaluate again (3rd time). See consult sent on 5/20/08, when the UFGD was October 15, 2008. **New UFGD is 1/15/09.** All labeling is available via EDR.

NAME AND PHONE NUMBER OF REQUESTER
Jena Weber, 301-796-1306

METHOD OF DELIVERY (Check one)
☒ DFS ONLY X HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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

/s/

Jena Weber
12/4/2008 12:25:25 PM

Weber, Jena M

From: Blay, Roy A
Sent: Friday, January 02, 2009 8:55 AM
To: Weber, Jena M
Subject: RE: NDA 20-866

Jena,

I believe you have copies of the letters sent to Drs. Fischer and Littlejohn. The inspection of Dr. Barengolts was completed and the inspector told me that there were no observations resulting from the inspection. I have not yet received the inspection report but anticipate that it will be an NAI classification. I will also be working on the inspection summary for you.

Please let me know if you need any other information at this time.

Roy

From: Weber, Jena M
Sent: Monday, December 29, 2008 8:58 AM
To: Blay, Roy A
Subject: NDA 20-866

Roy,

Looks like we just have 1 outstanding review from DSI on the Cycloset NDA. We are planning to take an action (AP) on/before Jan. 13th. Please let me know when to expect this.

Thanks,
Jena

ɔject Manager
/ision of Metabolism & Endocrinology Products
Jena.Weber@fda.hhs.gov
301-796-1306

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 20-866 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Cycloset
Established Name: bromocriptine mesylate tablets
Strengths: 0.8 mg
Applicant: VeroScience Inc.
Agent for Applicant: N/A

Date of Application: April 13, 2008
Date of Receipt: April 15, 2008
Date clock started after UN:
Date of Filing Meeting: June 4, 2008
Filing Date: June 15, 2008
Action Goal Date (optional): User Fee Goal Date: October 15, 2008

Indication requested: CYCLOSET is indicated as an adjunct to diet and exercise to improve glycemic control (hyperglycemia) in patients with type 2 diabetes mellitus (type 2 diabetes).
CYCLOSET is indicated as:

- Monotherapy in addition to diet and exercise.
- Adjunctive therapy in patients with type 2 diabetes mellitus who are failing therapy with insulin secretagogues (e.g. sulfonylurea) or metformin alone or another oral agent to improve glycemic control.
- Combination therapy with insulin if insulin alone does not provide adequate glycemic control.

Type of Original NDA:	(b)(1) X	(b)(2) ☐
AND (if applicable)		
Type of Supplement:	(b)(1) ☐	(b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification:	S		
Resubmission after withdrawal?	NO	Resubmission after refuse to file?	NO
Chemical Classification: (1,2,3 etc.)	3		
Other (orphan, OTC, etc.)	N/A		

Form 3397 (User Fee Cover Sheet) submitted: YES

User Fee Status: Paid ☐ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) X

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b).*

Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? NO
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  N/A

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? NO
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? NO

- Does the submission contain an accurate comprehensive index? NO
  If no, explain:

- Was form 356h included with an authorized signature? YES
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

  1. This application is a paper NDA NO

  2. This application is an eNDA or combined paper + eNDA YES
     This application is: All electronic ☐ Combined paper + eNDA ☐
     This application is in: NDA format ☐ CTD format ☐
     Combined NDA and CTD formats X

     Does the eNDA, follow the guidance?
     (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES

     If an eNDA, all forms and certifications must be in paper and require a signature.

     If combined paper + eNDA, which parts of the application were submitted in electronic format? All.

     Additional comments: Appropriate paper signatures obtained.

3. This application is an eCTD NDA. NO
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments: – **Noted and acknowledged.**

- Patent information submitted on form FDA 3542a? YES

- Exclusivity requested? _____ Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES

- Is this submission a partial or complete response to a pediatric Written Request? NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES

- PDUFA and Action Goal dates correct in tracking system? YES
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 34,661

- Are the trade, established/proper, and applicant names correct in COMIS? YES
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ NO
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? YES

- Risk Management Plan consulted to OSE/IO? YES

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES
  If no, did applicant submit a complete environmental assessment? YES
  If EA submitted, consulted to EA officer, OPS? YES

- Establishment Evaluation Request (EER) submitted to DMPQ? YES

- If a parenteral product, consulted to Microbiology Team? N/A

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 4, 2008

NDA 20-866

DRUG NAME: Cycloset (bromocriptine mesylate) tablets 0.8 mg

APPLICANT: VeroScience Inc.

BACKGROUND: NDA was submitted August 1997; an **approvable** letter was issued October 15, 1999. The company provided a complete response on April 13, 2008.

ATTENDEES: Drs. Joffe, Misbin, Pian, Sahlroot, Kuijpers, Choe, Vaidyanathan,Ysern, and Ms. Weber

ASSIGNED REVIEWERS (including those not present at filing meeting): Biswas, Blay, Carothers, Vishwanathan, Griffis, Lewin.

Discipline/Organization	Reviewer
Medical:	Joffe/Misbin
Secondary Medical:	NN
Statistical:	Sahlroot/Pian
Pharmacology:	Davis-Bruno/Kuijpers
Statistical Pharmacology:	NN
Chemistry:	Al-Hakim/Ysern
Environmental Assessment (if needed):	NN
Biopharmaceutical:	Choe/Vaidyanathan
Microbiology, sterility:	NN
Microbiology, clinical (for antimicrobial products only):	NN
DSI:	CLN, BPH (Blay, Vishwanathan)
OPS:	NN
Regulatory Project Management:	Aljuburi/Weber
Other Consults:	

Per reviewers, are all parts in English or English translation? YES
If no, explain:

CLINICAL FILE

- Clinical site audit(s) needed? YES
  If no, explain:
- Advisory Committee Meeting needed? _____ NO

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A

CLINICAL MICROBIOLOGY N/A

STATISTICS FILE

BIOPHARMACEUTICS FILE

- Biopharm. study site audits(s) needed? YES

PHARMACOLOGY/TOX FILE

- GLP audit needed? NO

CHEMISTRY FILE X REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES
- Sterile product? NO
  If yes, was microbiology consulted for validation of sterilization? N/A

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☐ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
Application poorly assembled, difficult to locate files, data, forms, etc.

X No filing issues have been identified.

☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. X If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

Jena M. Weber
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
(3) 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) 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, and.

(3) 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) 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, or

(3) 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 Office of Regulatory Policy representative.

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

*If "**No,**" skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES ☐ NO ☐

*If "**Yes,**" skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?

YES ☐ NO ☐

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No,**" to (a) skip to question 6. Otherwise, answer part (b and (c)).*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes,**" (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "**No,**" to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*
Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," to (c), proceed to question 7.*

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No**," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☐ NO ☐

*If "**No**," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

11. Is the application for a duplicate of a listed drug whose only difference is YES ☐ NO ☐

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☐

13. Which of the following patent certifications does the application contain? (Check all that apply <u>and</u> identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

  YES ☐ NO ☐

  *If "**Yes,**" what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*
  Was this listed drug product(s) referenced by the applicant? (see question # 2)

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

  N/A ☐ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☐

If "**Yes,**" please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

/s/

Jena Weber
12/29/2008 10:10:21 AM
CSO

12/27/08

Response to Email Request from Hylton Joffe of December 22, 1008 (attached hereto)

I. Rationale for Deferral Request

Product name: Bromocriptine-Quick Release (Cycloset)
IND/NDA/BLA number (as applicable): NDA 20-866
Applicant: VeroScience
Indications(s): Type 2 Diabetes
(NOTE: If drug is approved for or you are seeking approval for more than one indication, address the following for each indication.)

1. What pediatric age group(s) are included in your deferral request? **Age > 10 < 16 years**
2. Reason(s) for requesting deferral of pediatric studies (address each age group separately and for each age group — choose all that apply):
   - ✓ (a) Adult studies completed and ready for approval
   - (b) Additional postmarketing safety data needed (describe)
   - (c) Nature and extent of pediatric data needed (explain)
   - (d) Evidence provided of technological problems with development of a pediatric formulation
   - (e) Difficulty in enrolling pediatric patients (provide documentation)
   - (f) Other (specify)
3. What pediatric age group(s) is/are not included in your deferral request? **Ages 0 - 9**
4. Reason(s) for not including the pediatric age group(s) listed in number 3 in the deferral request (address each excluded age group separately and for each such age group — choose all that apply):
   - (a) Adequate pediatric labeling exists
   - (b) Studies completed in the specified age group
   - ✓ (c) **Requesting a waiver**
   - (d) Currently conducting pediatric studies that will be submitted with application
   - (e) Other (specify)
5. Has a pediatric plan been submitted to the Agency?
   - ☐ If so, provide date submitted.
   - ✓ If not, provide projected date pediatric plan is to be submitted.
     The anticipated time for the submission of the pediatric plan is within ——— of approval of Cycloset for the treatment of Type 2 diabetes in an adult patient population. b(4)
6. Suggested deferred date for submission of studies.

The anticipated time of the submission of the studies will be within ——— ——— of the marketing approval of Cycloset for the treatment of type 2 diabetes in an adult (>16 years of age) patient population. b(4)

7. Applicant certification. Richard Scranton MD MPH, Chief Medical Officer, VeroScience

14 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
OSE
Att. Cheryl Campbell

FROM: DMEP
Jena Weber, PM

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
12/18/08		20-866		4/13/08

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Bromocriptine mesylate	S	Anti-diabetic	**1/05/09**

NAME OF FIRM: VeroScience, LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- ☐ TYPE A OR B NDA REVIEW
- ☐ END OF PHASE II MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **Approvable letter issued on 10/15/1999.** Re-submission dated April 13, 2008. Please conduct post-marketing search for neuropsych events (events of special approach) - crude counting and data mining for bromocriptine mesylate, and evaluate as a safety review, not RMP.

NAME AND PHONE NUMBER OF REQUESTER
Jena Weber, 301-796-1306

METHOD OF DELIVERY (Check one)
☒ DFS ONLY

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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

/s/

Jena Weber
12/19/2008 01:53:49 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*:	FROM: DMEP
OSE **Att. Cheryl Campbell**	Jena Weber, PM

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
12/5/08		20-866	Tradename Proposal	4/13/08

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Bromocriptine mesylate	S	Anti-diabetic	12/29/08

NAME OF FIRM: VeroScience, LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **Approvable letter for this NDA issued on 10/15/1999.** At this time, the tradename "Cycloset," was acceptable. Please evaluate again (3rd time). See consult sent on 5/20/08, when the UFGD was October 15, 2008. New UFGD is 1/15/09. All labeling is available via EDR.

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
Jena Weber, 301-796-1306	☒ DFS ONLY X HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

X assignments to CC + rev. neuropsych

Do Post-M seeks events of special approach

Crude counting + data mining

use safety review not RMP.

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/s/

Jena Weber
12/4/2008 12:25:25 PM

VeroScience, LLC

1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

November 24, 2008

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

CDER/CDR
NOV 25 2008
RECEIVED

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Response to Issues and Questions for Cycloset Label
Amendment 41

Dear Dr. Parks,

Reference is made to an email (herewith attached) from our FDA project manager, Jena Weber, of November 6, 2008 requesting labeling changes and responses to FDA issues and questions regarding the Cycloset Label. This submission provides responses to that email request. This submission contains 1) the FDA letter specifying issues and questions of our draft Cycloset label with our responses to those issues and questions and related attachments thereto, 2) the revised, per FDA request, annotated label for Cycloset, and 3) the revised, per FDA request, un-annotated label for Cycloset.

FDA Form 356h and the above referenced email from Jena Weber follow this letter. We are providing an original (blue) archival copy, a clinical (tan) copy and three (black) desk copies of this submission. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta

Anthony H. Cincotta, PhD
President and Chief Scientific Officer

Weber, Jena M

From: Blay, Roy A
Sent: Wednesday, November 19, 2008 10:44 AM
To: Weber, Jena M
Subject: RE: Cycloset - NDA 20-866

Dear Jena,

I have completed my review of the inspection report for Dr. Fischer. It is a minor VAI, and the letter is currently under review by my supervisor (you'll get a copy of the letter as soon she signs off on the letter in DFS).

I am continuing to wait for the inspection report for Dr. Littlejohn. Again, a Form 483 was not issued, and it will probably be an NAI.

I have again requested an update of the inspection for Dr. Barengolts and am awaiting a response.

For the moment, the inspections have revealed nothing problematic. Should that change, I will alert you immediately. Please feel free to ask for updates as you need them.

Thanks for keeping in touch on this NDA.

Roy

From: Weber, Jena M
Sent: Wednesday, November 19, 2008 9:48 AM
To: Blay, Roy A
Cc: Misbin, Robert I
Subject: Cycloset - NDA 20-866

Roy,

n you please update me on the status of the clinical inspections for Cycloset.

Thanks,
Jena

Project Manager
Division of Metabolism & Endocrinology Products
Jena.Weber@fda.hhs.gov
301-796-1306

VeroScience, LLC

1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

November 12, 2008

ORIG AMENDMENT

N-000-BZ

DUPLICATE

RECEIVED

NOV 13 2008

CDR

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

11/19/08 To M. Gaffin + Champkell

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Response to Clinical and Container Label Requests
Amendment 40

Dear Dr. Parks,

Reference is made to 1) an email (herewith attached) from Dr. Misbin on November 7, 2008 requesting information on the concomitant diabetes medication changes for subjects during the Cycloset Safety Trial (Study Number 165-AD-04-03-US-1) and to 2) another email (herewith attached) from our project manager, Jena Weber, requesting copies of the carton and container labels for Cycloset. This submission provides responses to both of these email requests.

FDA Form 356h follows this letter. We are providing an original (blue) archival copy, a clinical (tan) copy and three (black) desk copies of this submission. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta

Anthony H. Cincotta, PhD
President and Chief Scientific Officer

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
SE
Att. Cheryl Campbell

FROM: DMEP
Jena Weber, PM

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
10/14/08		20-866	Labeling (PI, PPI, carton & container)	10/09/08

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Bromocriptine mesylate	S	Anti-diabetic	11/15/08

NAME OF FIRM: VeroScience, LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Labeling re-submission

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- ☐ TYPE A OR B NDA REVIEW
- ☐ END OF PHASE II MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Reference our DR letter sent 10/8/08, as per recommendations from OSE. Company has responded; please review and comment prn on all proposed LBL. Each section (PI, PPI, carton & container) is available via EDR dated 10/9/08.

NAME AND PHONE NUMBER OF REQUESTER
Jena Weber, 301-796-1306

METHOD OF DELIVERY (Check one)
☒ DFS ONLY X HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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

/s/

Jena Weber
10/14/2008 12:15:15 PM

ORIGINAL

VeroScience, LLC

1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

October 9, 2008

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

RECEIVED
OCT 10 2008
CDR

ORIG AMENDMENT

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Response to chemistry request for information on Cycloset stability data and analytical methods
Amendment 39

Dear Dr. Parks,

Reference is made to a phone call from Dr. Xavier Ysern, the FDA chemist reviewing our Cycloset NDA, on October 8, 2008. Dr. Ysern requested that we submit to the NDA a) stability data for the Cycloset drug product manufactured by PLIVA d.d. in Zagreb, Croatia and utilized in the Cycloset Safety Trial (study number 165-AD-04-03-US-1), b) recent stability data from at least one registration batch of Cycloset drug product manufactured by the proposed commercial manufacturer of Cycloset, Patheon Inc. for comparison to the PLIVA product stability data and c) information on the comparison of analytical methods historically used for analysis, identification and determination of bromocriptine and related compounds. We are herewith providing this information to the Chemistry section of NDA 20-866 in this submission as Amendment 39 to this NDA.

FDA Form 356h follows this letter. We are providing an original (blue) archival copy, a (red) chemistry copy, and three (black) desk copies of this submission. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta

Anthony H. Cincotta, PhD
President and Chief Scientific Officer

VeroScience, LLC

1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

October 9, 2008

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Response to DMEPA Instruction for Container Label and Package Insert Modifications
Amendment 38

Dear Dr. Parks,

Reference is made to the email communication from FDA to VeroScience on October 8, 2008 and its attached Discipline Review Letter (included herein) regarding DMEPA instructions for modifications to the Cycloset container labels and package insert. We have addressed the DMEPA instructions for modifications to the Cycloset label and package insert in this Amendment 38 to NDA 20-866. The modified package insert per DMEPA instruction is included in this submission as both a WORD document and in SPL format and both are electronic submissions on a single disc. We have also included these package insert modifications as a paper submission. Finally, we have made the changes to the retail and physician container labels as instructed and these new labels are submitted in paper form and also electronically on the same disc with the modified package insert.

FDA Form 356h and the above referenced email communication from FDA follow this letter. The enclosed information disk was scanned with Symantec Antivirus Version 10.1.0.394 Scan Engine 81.2.0.25 Virus Definition File Version 10/9/2008 rev 3 and found to be virus-free. We are providing an original (blue) archival copy, a (tan) clinical copy, and three (black) desk copies of this submission. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta

Anthony H. Cincotta, PhD
President and Chief Scientific Officer

ORIGINAL

VeroScience, LLC

1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

October 8, 2008

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

RECEIVED
OCT 09 2008
CDR
N. 000 (AW)
ORIG AMENDMENT

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Pediatric Partial Waiver and Deferral for Cycloset in the Treatment of Type 2 Diabetes
Amendment 36

Dear Dr. Parks,

Reference is made to the attached email communication to VeroScience from FDA dated July 23, 2008 wherein FDA requested the submission of either a pediatric drug development plan or a request for pediatric waiver/deferral for Cycloset use in the treatment of type 2 diabetes in children/adolescents.
This Amendment 36 is submitted to comply with the Pediatric Research Equity Act (Public Law 108-155) (PREA) following the recommendations in the FDA Guidance for Industry - draft guidance of September 2005 on How to Comply with the Pediatric Research Equity Act. We are herein requesting a partial waiver of the requirement to submit pediatric assessments for Cycloset in the treatment of type 2 diabetes with respect to infants and children ages [redacted] years and a deferral of the requirement to submit pediatric assessments for Cycloset in the treatment of type 2 diabetes with respect to adolescents ages [redacted] years. The justification and rationale for submitting such a partial waiver/deferral request are succinctly delineated within this submission utilizing the query- answer format recommended and supplied in the aforementioned draft guidance. b(4)

We are providing an original (blue) archival copy, a clinical (tan) copy and three desk (black) copies for FDA. Form 356h and a copy of the above referenced FDA - VeroScience email communication follow this letter. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta

Anthony H. Cincotta, PhD
President and Chief Scientific Officer

I. Rationale for Deferral Request

Product name: Bromocriptine [redacted] (Cycloset) b(4)
IND/NDA/BLA number (as applicable): NDA 20-866
Applicant: VeroScience
Indications(s): Type 2 Diabetes
(NOTE: If drug is approved for or you are seeking approval for more than one indication, address the following for each indication.)

1. What pediatric age group(s) are included in your deferral request? **Age > 10 < 18 years**
2. Reason(s) for requesting deferral of pediatric studies (address each age group separately and for each age group — choose all that apply):
   - ✓ (a) Adult studies completed and ready for approval
   - (b) Additional postmarketing safety data needed (describe)
   - (c) Nature and extent of pediatric data needed (explain)
   - (d) Evidence provided of technological problems with development of a pediatric formulation
   - (e) Difficulty in enrolling pediatric patients (provide documentation)
   - (f) Other (specify)
3. What pediatric age group(s) is/are not included in your deferral request? **Ages 0 - 10**
4. Reason(s) for not including the pediatric age group(s) listed in number 3 in the deferral request (address each excluded age group separately and for each such age group — choose all that apply):
   - (a) Adequate pediatric labeling exists
   - (b) Studies completed in the specified age group
   - ✓ (c) **Requesting a waiver**
   - (d) Currently conducting pediatric studies that will be submitted with application
   - (e) Other (specify)
5. Has a pediatric plan been submitted to the Agency?
   - ☐ If so, provide date submitted.
   - ✓ If not, provide projected date pediatric plan is to be submitted.
     The anticipated time for the submission of the pediatric plan is [redacted] of approval of Cycloset for the treatment of Type 2 diabetes in an adult patient population. b(4
6. Suggested deferred date for submission of studies.

The anticipated time of the submission of the studies will be [redacted] years of the marketing approval of Cycloset for the treatment of type 2 diabetes in an adult (>18 years of age) patient population. b(4

7. Applicant certification.

Richard Scranton MD MPH, Chief Medical Officer

VeroScience

1 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Product name: Bromocriptine _____ **(Cycloset)** b(4)
IND/NDA/BLA number (as applicable): NDA 20-866
Applicant: VeroScience
Indications(s): Type 2 Diabetes

1. Identify pediatric age group(s) included in your waiver request. b(4)
   Waiver request for Infants and children aged _____

2. With regard to each age group for which a waiver is sought, state the reason(s) for waiving pediatric assessment requirements with reference to applicable statutory authority (i.e., one of the options (a)-(d) listed below — choose all that apply):

✓ **(a)Studies are impossible or highly impractical (because the number of Pediatric patients in this age group are very small to non-existent). If applicable, please check from the following list of adult-related conditions that may qualify the drug product for disease-specific waivers:**

__ Age-related macular degeneration
__ Alzheimer's disease
__ Arteriosclerosis
__ Infertility
__ Amyotrophic lateral sclerosis
__ Menopause symptoms

__ Osteoarthritis
__ Parkinson's disease
X Other (please state and justify)
Type 2 Diabetes – adult onset diabetes mellitus

__ Basal cell and squamous cell cancer
__ Breast cancer
__ Colorectal cancer
__ Endometrial cancer
__ Hairy cell cancer
__ Lung cancer (small cell and non-small cell)
__ Oropharynx cancers (squamous cell)
__ Ovarian cancer (non-germ cell)
__ Pancreatic cancer
__ Prostate cancer
__ Renal cell cancer
__ Uterine cancer

(b) The product would be ineffective or unsafe in one or more of the pediatric age group(s) for which a waiver is being requested.
(c) The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
(d) Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. Please document previous attempts to make a pediatric formulation and describe reasons for failure.

3. Provide evidence that the statutory reason(s) for waiver of pediatric studies have been met (not necessary if a 2(a) category is checked).

Justification for Pediatric waiver for children aged —— b(4)

Only recently has type 2 diabetes become a reality for children aged 10-18 years. The US SEARCH study (population based study of diabetes in children across six centers) identified 6379 children or adolescents with any type of diabetes from ~3.5 million youth. In this study, among younger children with diabetes, ≥ 80% were type 1 diabetics in contrast to older youth where the proportion of diabetic children with type 2 diabetes ranged from 6% in non-Hispanic whites to 76% in American Indians. According to the American Academy of Pediatrics, in 2001 the prevalence of type 2 diabetes cases per 1000 youth in all age groups from birth to age 19 was 0.22. The highest prevalence was among American Indian youths aged 10-19 at 1.74 per 1000. The Academy states that this was the largest surveillance effort on diabetes in youth at the time.[1]

Although the incidence of type 2 diabetes appears to be on the rise,[2] the absolute number of youth with type 2 diabetes is still very small. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) are currently recruiting children 10-17 years of age for the TODAY study. Less than 500 subjects have been recruited since May 2004. The study hopes to enroll a total of 750 subjects in time to publish results by 2011.[3] This study confirms the focus on children aged >10 where the prevalence of type 2 diabetes is increasing. The ADA consensus statement of 2000 supports this approach as evident by the following statement "Currently, children with type 2 diabetes are usually diagnosed over the age of 10 years and are in middle to late puberty. As the childhood population becomes increasingly overweight, type 2 diabetes may be expected to occur in younger prepubertal children." Although epidemiology studies of the prevalence of type 2 diabetes in children are limited, the available evidence suggests that the incidence is for the most part nearly non-existent for children under the age of 10 years (see table 1).

[1] American Academy of Pediatrics (2006) The burden of diabetes mellitus among US youth: prevalence estimates from the search for diabetes in youth study. *Pediatrics* 118; 1510-1518
[2] http://www.cdc.gov/diabetes/projects/cda2.htm

[3] ClinicalTrials.gov NCT00081328

Since the prevalence of type 2 diabetes in children is still relatively small in comparison to the adult population, studies of pharmacological interventions for the treatment of type 2 diabetes in an adolescent population are limited primarily to children over the age of 10 years. There was however a study of 285 subjects that compared the efficacy and safety of glimepiride or metformin in children with type 2 diabetes mellitus (T2DM) (age 8-17 years). The primary endpoint was mean change in HbA1c from baseline to week 24 and safety was assessed by incidence of hypoglycemia and other adverse events. Subjects with type 2 diabetes and HbA1c between 7.1% and 12.0% were randomized to either glimepiride or metformin for 24 weeks. A total of 78.0% of the glimepiride group and 81.7% of the metformin group completed the study. The authors concluded that glimepiride was safe and effective for use in this population over 24 weeks, but further studies are warranted to determine the best approach to treatment using a combination of diet, exercise and oral anti-hyperglycemic therapy. The study was supported by Sanofi-Aventis, makers of glimepiride and results were published in 2007. [4] Two more recently approved therapies for the treatment of type 2 diabetes have been utilized in investigational studies in children > 10 years of age. For example, exenatide was used in a completed phase 2 study in children aged 10-16 and is also being used in another study that is currently recruiting children with T2DM aged 10-16 years (phase 3). Sitagliptin is being utilized in one ongoing (phase 1) study in patients with T2DM aged 10-17. Currently, there are no investigational studies registered in www.clincaltrial.gov for children with type 2 diabetes under the age of 10.

Based on our review of current literature and expert opinion, the primary intervention in children (age <10 years) with type 2 diabetes is lifestyle change, including diet and exercise changes. The relatively low (or nearly non-existent) incidence of type 2 diabetes in the pediatric (age <10 years) population coupled with the fact that the primary current recommended treatment modality for the disease is and will continue to be diet and exercise serve as the justification for a partial pediatric waiver for Cycloset for this indication in this subject population.

[4] Gottschalk, M. et al. (2007, April) Glimeperide versus metformin as monotherapy in pediatric patients with type 2 diabetes. Diabetes Care; vol. 30, number 4.

VeroScience, LLC

1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

October 8, 2008

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Approvable Letter – Pharmacology and Toxicology Question Response
Amendment 37

Dear Dr. Parks,

At this time we are filing an amendment (Amendment 37) to our pending NDA to resolve an oversight regarding a response to one preclinical question listed in the Approvable Letter issued by the Agency on October 15, 1999.

On April 13, 2008 we filed an amendment (Amendment 29) to provide a Complete Response to all outstanding issues listed in the approvable letter, referenced above. On October 3, 2008, a call was received from Dr. Gemma Kuijpers of FDA requesting further information regarding impurities in the Cycloset drug product. Dr. Kuijpers was informed about where to find the information relating to the impurities in the Cycloset drug product in the original NDA (Volume 4 page 090, Section 4.3.7.1) and in Amendment 29 to the NDA (Volume 3 page 408; Section 4.3.7); however, in reviewing the submission after the telephone call, we have realized that we inadvertently omitted a formal response to Question 4 in the Approvable letter regarding impurities in the drug substance/API. The response should have been provided in Section 5 of Amendment 29. At this time we are correcting that omission.

In the original NDA filing, two impurities were identified in the API produced by ——— b(4)
These impurities were identified as Compounds A and B and both were concluded to be brominated alpha- ergocryptine analogs. Compounds A and B were individually tested to assess mutagenic potential and were shown to be negative for inducing forward mutations at the TK locus in L51798Y mouse lymphoma cells under activated and non-activated conditions and these data appear in the original NDA - nonclinical pharmacology and toxicology section (Volume 7 pages 083-095). These impurities however, were not found in our studies in the bromocriptine API from ——— b(4)
——— We

are currently using only [redacted] as a source for bromocriptine API. The Cycloset safety trial used drug product made with only [redacted] and NDA Amendment 29 contains information covering manufacturing of drug product using only [redacted] No drug product is being or will be produced with API from [redacted] The amounts of impurities in the [redacted] as listed in the current NDA filing (Amendment 29 to NDA 20-866, Volume 3 pages 010-016; Section 4.2) are [redacted] Although these impurities are not identified, they are below the ICH limit of 0.1% for qualification. b(4) b(4)

FDA Form 356h follows this letter and a certification that no [redacted] will be used for production of Cycloset follows the FDA form. We trust that this amendment will complete the issues related to the preclinical update to our NDA. We are providing an original (blue) archival copy, a yellow (pharmacology/toxicology) copy, a red (chemistry/manufacturing controls) copy and two (black) desk copies of this submission. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com. b(4)

Sincerely,

Anthony H. Cincotta

Anthony H. Cincotta, PhD
President and Chief Scientific Officer

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-866

DISCIPLINE REVIEW LETTER

VeroScience, LLC
Attention: Anthony Cincotta, Ph.D.
President and CSO
1334 Main Road
Tiverton, RI 02878

10/8/08

Dear Dr. Cincotta:

Please refer to your April 13, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cycloset (bromocriptine mesylate quick release) Tablets 0.8 mg.

The Division of Medication Error Prevention and Analysis (DMEPA) has completed their review of your submission, and has the following comments and requests. Please address these in writing to your NDA file.

Proprietary Name

DMEPA currently has no objections to the use of the proprietary name, Cycloset. DMEPA will request another review of the proprietary name if approval of the NDA is delayed beyond 90 days from the date of the completed initial review (September 26, 2008) to ensure that there are no changes in healthcare practices or drug product characteristics that could increase vulnerability of the proposed name to confusion.

Retail and Physician Container Labels

1. The size of the company name and logo should be decreased so as not to interfere with the readability of the proprietary name and strength.

2. In accordance with 21 CFR 201.10(g)(2), the prominence of the established name should be increased to at least ½ the size of the proprietary name, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. We note that in some of the labels, the established name appears to be of adequate size but in other labels, it does not. Since the proprietary name for this product is bolded in the labels, the size of the established name may need to be increased more than ½ the size of the proprietary name to satisfy this requirement.

3. Relocate the net quantity statement to an area on the label that doesn't intervene with the dosage strength statement (i.e. upper or bottom corner of the principle display panel).

Package Insert

In the Patient Counseling Sections of labeling (sections 2.1, 17.1 and 17.3), patients are instructed to take their morning dose of Cycloset between 8 am and 10 am. Depending on an individual patient's sleeping patterns, listing specific times for dose administration could create confusion for the patient and lead to possible missed doses. The specific time to administer the dose should be omitted (unless there is a compelling reason not to), and these sections of labeling should be revised to be consistent with the **DOSAGE AND ADMINISTRATION** section of labeling which states to take the recommended dose of Cycloset within 2 hours after waking in the morning.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
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/

Mary Parks
10/8/2008 10:59:58 AM

ORIGINAL AMENDMENT ORIGIN

VeroScience, LLC

1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

October 6, 2008

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

RECEIVED
OCT 07 2008
CDR

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Subject Data for Insulin Sensitivity Study (Study Number 1-96-2.2) – Submission of Electronic Copy
Amendment 35

Dear Dr. Parks,

Reference is made to the attached email communication to VeroScience from FDA requesting an electronic copy of subject data from the insulin sensitivity study report (Study Number 1-96-2.2) submitted in Amendment 33 to the Cycloset NDA 20-866. We are herewith providing those requested data in electronic format on disc in this Amendment 35 to the NDA. The data tables on disc are in Microsoft Excel application program that can be imported into SAS programs. We note that in Amendment 33, we had inadvertently omitted a re-formatted table of the original data that itself is located within that submission (First Step of the Hyperinsulinemic – Euglycemic Clamp; pages 009 and 013 of Amendment 33) and are including it here in electronic format (Table title in this Amendment 35 submission: Table 3. Cycloset Influence on Insulin Sensitivity: First Step of the Hyperinsulinemic – Euglycemic Clamp).

We are providing an original (blue) archival copy that includes the requested data disc for FDA. This disk was scanned with Symantec Antivirus Version 10.1.0.394 Scan Engine 81.2.0.25 Virus Definition File Version 10/06/2008 rev 6 and found to be virus-free. Form 356h and a copy of the above referenced FDA - VeroScience email communication follow this letter. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta

Anthony H. Cincotta, PhD
President and Chief Scientific Officer

VeroScience, LLC

1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

September 4, 2008

DUPLICATE

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

RECEIVED
SEP 05 2008
CDR NEW CORRESP

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Outline of Proposed Post-approval Pharmacovigilance Plan for Cycloset for the Treatment of Type 2 Diabetes
Amendment 32

Dear Dr. Parks,

Reference is made to email communications to VeroScience from FDA between the dates of June 6 and August 27, 2008 (attached hereto) regarding the Agency's instruction for submission of a proposed post-approval phamacovigilance plan for Cycloset to be included in the Cycloset NDA 20-866. The conclusion of these communications was that VeroScience would submit a detailed outline/overview of a proposed pharmacovigilance plan to be reviewed by the Agency for its possible comments and recommendations that in turn would then be incorporated into a final pharmacovigilance plan for Cycloset by VeroScience and submitted to FDA. This NDA 20-866 Amendment 32 submission provides the FDA-requested detailed outline/overview of the VeroScience proposed pharmacovigilance plan for Cycloset. Of note, this proposed pharmacovigilance plan [redacted] b(4)

[redacted] b(4) We look forward to the Agency's prompt review of and comments on the enclosed outline of the proposed pharmacovigilance plan so that we may move forward with the final pharmacovigilance safety program submission to FDA as soon as possible.

We are herewith providing an original copy along with 4 additional desk copies of this paper submission. Form 365h and a copy of the above referenced FDA - VeroScience email communications between June 6 and August 27, 2008 follow this letter. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email me at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta

Anthony H. Cincotta, PhD
President and Chief Scientific Officer

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT VeroScience LLC	DATE OF SUBMISSION 09/04/2008
TELEPHONE NO. *(Include Area Code)* 401-816-0525	FACSIMILE *(FAX)* Number *(Include Area Code)* 401-608-3079
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 1334 Main Road, Tiverton, RI 02878	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone number)* IF APPLICABLE

RECEIVED
SEP 05 2008
CDR

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 20-866

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* bromocriptine mesylate	PROPRIETARY NAME *(Trade name)* IF ANY Cycloset

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* (5'α)-2-Bromo-12'-hydroxy-2'-(1-methylethyl)-5'-(2-methylpropyl)ergotaman-3',6',18-trione	CODE NAME *(If any)*

DOSAGE FORM: tablet	STRENGTHS: 0.8 mg	ROUTE OF ADMINISTRATION: oral

(PROPOSED) INDICATION(S) FOR USE:
Treatment of Type 2 Diabetes Mellitus

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Submission of Detailed Outline of Proposed Post-approval Pharmacovigilance Plan

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 34,661

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Submission of Detailed Outline of Proposed Post-approval Pharmacovigilance Plan

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Anthony H. Cincotta	Anthony H. Cincotta, Ph.D., President and CSO	09/04/2008

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
1334 Main Road, Tiverton, RI 02878	(401) 816-0525

Public reporting burden for this collection of information is estimated to average 24 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:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

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.

Anthony Cincotta

From: Weber, Jena M [jena.weber@fda.hhs.gov]
Sent: Wednesday, August 27, 2008 11:12 AM
To: Anthony Cincotta
Subject: RE: Cycloset

Anthony,

Please submit your draft plan as an amendment to your NDA file. After the clinical and safety reviewers within our Division evaluate it, I will consult OSE for their input. From there, we will determine if a meeting (or t-con) should be scheduled.

Also, in reference to the e-mail that I sent to you yesterday (8/26), please reply in writing to the Cycloset NDA.

Thanks,
Jena

From: Anthony Cincotta [mailto:Anthony_Cincotta@veroscience.com]
Sent: Monday, August 25, 2008 12:07 PM
To: Weber, Jena M
Subject: RE: Cycloset

Dear Jena,

We are now finalizing our detailed overview of our proposed Cycloset Pharmacovigilance Plan for FDA review and I believe we will be submitting it to FDA within a week. Should we submit the overview as an amendment to the NDA or as an FDA communication? Can you give any guidance as how to proceed from here with this matter?

As mentioned in my previous email communications below, we would like to have a meeting with the appropriate Divisions at FDA to gain their input and guidance on our proposed pharmacovigilance plan before submitting the final full plan. Should we, subsequent to our submission of the overview, make a request for such a meeting to the Division Director, Dr. Parks? Your guidance here would be greatly appreciated.

Regards,
Anthony

From: Weber, Jena M [mailto:jena.weber@fda.hhs.gov]
Sent: Tuesday, June 10, 2008 10:43 AM
To: Anthony Cincotta
Cc: Misbin, Robert I
Subject: RE: Cycloset

Sounds good. Please provide draft plan.

Jena

From: Anthony Cincotta [mailto:Anthony_Cincotta@veroscience.com]
Sent: Tuesday, June 10, 2008 10:36 AM
To: Weber, Jena M
Subject: RE: Cycloset

Jena,

Very well . Please let me know if and when we need to submit the Pharmacovigilance Plan draft to initiate a dialogue with FDA on its final format. For now we will await your response from OSE as how to move forward. We were proceeding from the guidances to industry from FDA on this as I mentioned in my last email and can provide a draft Pharmacovigilance Plan within a short period of time from when you instruct us to do so. Is this OK?.

Best,
Anthony

From: Weber, Jena M [mailto:jena.weber@fda.hhs.gov]
Sent: Monday, June 09, 2008 2:46 PM
To: Anthony Cincotta
Subject: RE: Cycloset

Thanks for your response. I am sending out consults to the appropriate Divisions that need to be involved in the review of your NDA. I just did not see a specific tab for the RMP, so I wanted to make sure that I was not missing something. I will ask OSE to review what you have submitted and go from there.

Thanks,
Jena

From: Anthony Cincotta [mailto:Anthony_Cincotta@veroscience.com]
Sent: Monday, June 09, 2008 2:16 PM
To: Weber, Jena M
Subject: RE: Cycloset

Jena,

We did not submit a Risk Management Plan (RMP) for the Cycloset NDA with the Complete Response to the approvable letter inasmuch as we are planning to incorporate any relevant aspects of a RMP into our Pharmacovigilance Plan and are expecting input and recommendations from FDA on the construct of this Pharmacovigilance Plan based upon its conclusions on Cycloset safety drawn from data within our Complete Response amendment (#29). The FDA guidances on Development and Use of Risk Minimizing Action Plans (Section VI) and on development of Pharmacovigilance Plans recommend an ongoing dialogue between the Agency and the sponsor to construct an appropriate RMP or Pharmacovigilance Plan. We have every intention of working with the FDA to construct a responsible pharmacovigilance plan for Cycloset, incorporating reasonable elements of design as potentially recommended by the FDA subsequent to its review of the Complete Response. If the division would like to accelerate the dialogue on this matter, we are ready and willing to begin such discussions now. We look to your instruction on the time table and process for doing so.

The Complete Response includes the results from a large (3070 subject), randomized clinical trial on safety of Cycloset, analyses from World Health Organization and FDA pharmacovigilance databases on adverse experiences encountered with the use of the active ingredient in Cycloset, bromocriptine mesylate, dating back over 30 years of its world-wide use, a literature review of any such adverse experiences, and a retrospective analysis of cardiovascular events of subjects within the UK GPRD database exposed to bromocriptine mesylate. The conclusions of the sponsor on the safety and efficacy of Cycloset are delineated in the Overall Summary of Safety and the Overall Summary of Efficacy, respectively, within the Complete Response. Also, the benefit/risk profile of the drug and recommendations for its use are detailed in the Package Insert (Label) for the drug within the amendment. VeroScience has every intent to ensure maximized physician education and awareness of the therapeutic profile for Cycloset for appropriate prescribing of this drug and to ensure earnest efforts to maximize patient safety regarding its use.

Please instruct us on how best to move forward with this aspect of our application review and what steps we can take to facilitate the process (i.e., should we provide a draft of a Pharmacovigilance Plan in the near future prior to meeting with FDA on the matter?).

Best,
Anthony

From: Weber, Jena M [mailto:jena.weber@fda.hhs.gov]
Sent: Friday, June 06, 2008 9:22 AM
To: Anthony Cincotta
Subject: Cycloset

Anthony,

Did you submit a specific Risk Management Plan for the Cycloset NDA, or is it part of Pharmacovigilance?

Thanks,
Jena

Project Manager
Division of Metabolism & Endocrinology Products
Jena.Weber@fda.hhs.gov
301-796-1306

34 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Jena Weber
10/1/2008 08:51:40 AM

VeroScience, LLC

1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

September 24, 2008

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Supplemental Analysis of Primary Safety and Composite Cardiovascular Endpoint from Study No. 165-AD-04-03-US-1 (Cycloset Safety Trial)
Amendment 34

Dear Dr. Parks,

Reference is made to the attached email communications between VeroScience and FDA regarding a supplemental analysis of primary safety and composite cardiovascular endpoint from Study No. 165-AD-04-03-US-1 (Cycloset Safety Trial). In an email to Dr. Misbin at FDA dated July 18, 2008, VeroScience had indicated that it had conducted a supplemental analysis of the primary safety and composite cardiovascular endpoint inclusive of "on-treatment plus off-treatment" subject time during the study period for subjects in the Cycloset Safety Trial and that the results of this analysis recapitulate the findings and conclusions of those presented in the Cycloset Safety Trial Clinical Study Report (Amendment 27 to NDA 20-866). Dr. Misbin indicated that there would be value in submitting this analysis to the NDA and therefore this Amendment 34 to the NDA contains the report of that supplemental analysis. The Appendices for this paper report, including the analytical dataset thereof, are on discs submitted in a separate volume from the paper report. These disks were scanned with Symantec Antivirus Version 10.1.0.394 Scan Engine 81.2.0.25 Virus Definition File Version 9/23/2008 rev 3and found to be virus-free.

Also included in this submission are copies of the tables and figures from Amendments 27 and 29 to this NDA that were recently submitted electronically to Dr. Misbin per his request (see attached email).

We are providing an original (blue) archival copy, a clinical (tan) copy, a statistics (green) copy, and two additional (black) desk copies of this Amendment 34 for FDA. Form 365h and a copy of the above referenced FDA - VeroScience email communications follow this letter. If you have any

questions regarding this submission, please feel free to contact me by phone at 617 966 8413, by fax at 401 608 3079 or by email at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta

Anthony H. Cincotta, PhD
President and Chief Scientific Officer

VeroScience, LLC

1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

September 19, 2008

RECEIVED
SEP 22 2008
CDER CDR

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Response to Information Request – Subject Data for Insulin Sensitivity Study (Study Number 1-96-2.2)
Amendment 33

Dear Dr. Parks,

Reference is made to the attached email communication to VeroScience from FDA regarding an Information Request for subject data from the insulin sensitivity study report (Study Number 1-96-2.2) submitted in Amendment 29 (Volume 17) to the Cycloset NDA 20-866. We are herewith providing those requested data in this Amendment 33 to the NDA. These data were originally submitted to FDA under IND 34,661 Annual Report serial number 199 (which contained the entire study report) but they were inadvertently omitted from the NDA filing of this study report in the Amendment 29 NDA submission. For completeness sake, in addition to providing the specific data requests of FDA from this study report, we have also included the original complete data pages from the IND filing of this study report from which the requested data were extracted.

We are providing an original (blue) archival copy, a clinical (tan) copy, a statistics (green) copy, and two additional (black) desk copies for FDA. Form 365h and a copy of the above referenced FDA - VeroScience email communication follow this letter. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email me at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta

Anthony H. Cincotta, PhD
President and Chief Scientific Officer

VeroScience, LLC

1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

September 4, 2008

DUPLICATE

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

RECEIVED
SEP 05 2008
CDR

N-020C
NEW CORRESP

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Outline of Proposed Post-approval Pharmacovigilance Plan for Cycloset for the Treatment of Type 2 Diabetes
Amendment 32

Dear Dr. Parks,

Reference is made to email communications to VeroScience from FDA between the dates of June 6 and August 27, 2008 (attached hereto) regarding the Agency's instruction for submission of a proposed post-approval phamacovigilance plan for Cycloset to be included in the Cycloset NDA 20-866. The conclusion of these communications was that VeroScience would submit a detailed outline/overview of a proposed pharmacovigilance plan to be reviewed by the Agency for its possible comments and recommendations that in turn would then be incorporated into a final pharmacovigilance plan for Cycloset by VeroScience and submitted to FDA. This NDA 20-866 Amendment 32 submission provides the FDA-requested detailed outline/overview of the VeroScience proposed pharmacovigilance plan for Cycloset. Of note, this proposed pharmacovigilance plan [redacted] b(4)

[redacted] We b(4)
look forward to the Agency's prompt review of and comments on the enclosed outline of the proposed pharmacovigilance plan so that we may move forward with the final pharmacovigilance safety program submission to FDA as soon as possible.

We are herewith providing an original copy along with 4 additional desk copies of this paper submission. Form 365h and a copy of the above referenced FDA - VeroScience email communications between June 6 and August 27, 2008 follow this letter. If you have any questions regarding this submission, please feel free to contact me by phone at 617 966 8413 or by fax at 401 608 3079 or by email me at: Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta

Anthony H. Cincotta, PhD
President and Chief Scientific Officer

DSI CONSULT: Request for Clinical Inspections

Date:	June 10, 2008
To:	Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46 Joe Salewski., Branch Chief (Acting), GCP2, HFD-47 Name of DSI Primary Reviewer
Through:	Robert Misbin, M.D., Review Division/HFD-510 Hylton Joffe, M.D. Teamleader, Review Division/HFD-510 Mary Parks, M.D., Division Director, DMEP
From:	Jena Weber, Regulatory Health Project Manager/Division/HFD-510
Subject:	**Request for Clinical Site Inspections**

I. General Information

Application: NDA 20-866
Sponsor: VeroScience, Anthony Cincotta, Ph.D., President, CSO 401-816-0525
Drug: Cycloset (bromocriptine mesylate) Tablets
NME: No
Standard (6-month clock)
Pediatric exclusivity: No

PDUFA: October 15, 2008
Action: October 15, 2008
Inspection Summary Goal Date: October 1, 2008

II. Background Information

Include a brief introduction about the application and include the following:

- *New application (re-submission)*
- *Proposed indication: Type 2 Diabetes Mellitus*
- *Brief information*
  - *on drug*
  - *disease*
  - *pivotal studies (large clinical trial, Study 165-AD-04-03-US-1)*

Protocol/Site Identification

Include the Protocol Title/# for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
Site 180, Jerome Fischer DGD Research Inc. 803 Castroville Road, Suite 140 San Antonio, TX 78237	165-AD-04-03-US-1	81	Type 2 Diabetes Mellitus
Site 215, Charles Herring, M.D. New Hanover Medical Research, 1907 Tradd Court, Wilmington, NC 28410	165-AD-04-03-US-1	157	Type 2 Diabetes Mellitus
Site 260, Thomas Littlejohn, M.D., Piedmont Medical Research, 1901 S. Hawthorne Road, Suite 306, Winston-Salem, NC 27103	165-AD-04-03-US-1	152	Type 2 Diabetes Mellitus
Site 350, Sherwyn Schwartz, M.D., DGD Research Inc. 5107 Medical Drive San Antonio, TX 78229	165-AD-04-03-US-1	183	Type 2 Diabetes Mellitus
Site 537, Elena Barengolts, M.D., Chicago Westside VAMC, CHCS Westside, 820 S. Damien Ave., M/C111, Chicago, IL 60654	165-AD-04-03-US-1	136	Type 2 Diabetes Mellitus

III. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Things to consider in decision to submit request for DSI Audit

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*

- *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
- *Expected commonly reported AEs are not reported in the NDA*

- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

Rationale for DSI Audits

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

Domestic Inspections:

Reasons for inspections (please check all that apply):

X___ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
X___ **Other: Please evaluate 3 out of the 5 investigators specified.**

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact *Name of RPM* at Ph: *301-796-xxxx or Name of Medical Officer* at Ph: 301-796-XXXX.

Concurrence: (as needed)

_____ Medical Team Leader
_____ Medical Reviewer
_____ Director, Division Director (for foreign inspection requests only)

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/s/

Mary Parks
8/13/2008 02:39:09 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-866

INFORMATION REQUEST LETTER

VeroScience, LLC
Attention: Anthony H. Cincotta, Ph.D.
President and CSO
1334 Main Road
Tiverton, RI 02878

Dear Dr. Cincotta:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Cycloset (bromocriptine mesylate) Tablets.

We also refer to your submission dated April 13, 2008.

We are reviewing the Clinical and Statistical sections 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. Additional issues may be identified during the review process, and may be added, deleted, expanded upon, or modified.

1. For the primary safety endpoint and all secondary safety endpoints, we request time-to-event data with censoring variable and a variable for exposure (adjusted person years) for each patient.

2. The datasets should include all randomized patients, not just those patients with events. Demographic and baseline characteristics should be included e.g., treatment group, indicator variables for metformin use, sulfonylurea use, metformin and sulfonylurea use, insulin use, as well as center, VA or non-VA, etc.

3. For the secondary safety endpoint of composite CVD, please provide variables that enable the analysis of individual endpoints in the composite as well as the composite endpoint itself.

4. Due to difficulties in working with the submitted electronic data files, the Statistics team may be requesting more specific and user-friendly datasets in addition to those requested above as the review progresses.

5. All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. Please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver/deferral is appropriate. In your request, you should summarize the effects on maturation, reproductive function, behavioral effects etc. that might be expected to occur in children.

Please respond only 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 me at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Jena M. Weber
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
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/

Jena Weber
7/23/2008 01:06:00 PM

For Consulting Center Use Only:
Date Received: _____
Assigned to: _____
Date Assigned: _____
Assigned by: _____
Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center): Lori Tull, CBER
Center: OCTGT
Division: DCEPT
Mail Code: HFM-755
Consulting Reviewer Name: Bruce Schneider, M.D.
Building/Room #: WOC 1, 213-S
Phone #: 301-827-8343
Fax #:
Email Address: Bruce.Schneider@fda.hhs.gov

From (Originating Center): CDER, Jena Weber
Center: ODS II
Division: DMEP
Mail Code: HFD-510
Requesting Reviewer Name: Robert Misbin, M.D.
Building/Room #: WO, Bld. 22, #3120
Phone#: 301-796-1259
Fax #: 301-796-0712
Email Address:Robert.Misbin@fda.hhs.gov
Requesting Reviewer's Concurring: DFS
Supervisor's Name: DFS

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: July 3, 2008
Submission/Application Number: 20-866

Requested Completion Date: Sept. 15, 2008
Submission Type: RS

Type of Product: Drug-device combination
Device-biologic combination
Not a combination product X

Drug-biologic combination
Drug-device-biologic combination

Submission Receipt Date: April 13, 2008

Official Submission Due Date: April 15, 2008

Name of Product: Cycloset (bromocriptine maleate)
Name of Firm: VeroScience
Intended Use: type 2 DM

Brief Description of Documents Being Provided Clinical data, **3 volumes for review of Dr. DeFronzo's clamp study.**

Documents to be returned to Requesting Reviewer? **Yes**

Complete description of the request. Approvable letter for this NDA issued on 10/15/1999. As requested by Dr. Misbin, please review and comment on Dr. DeFronzo's clamp study (1-96-2.2). Hard copies to be delivered. **UFGD is October 15, 2008.**

Type of Request: **Consultative Review.**

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/s/

Mary Parks
7/8/2008 11:15:34 AM

VeroScience, LLC
1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

June 25, 2008

NDA 020-C

RECEIVED
JUN 26 2008
CDER CDR

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 – Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

ORIGINAL

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Datasets for Efficacy Analyses from Cycloset Safety Trial – (Report Number 165-AD-04-03-US-1)
Amendment 30

Dear Dr. Parks,

Reference is made to our previous Amendments 27 (the Clinical Study Report for the Cycloset Safety Trial), 28 (the complete data sets for the Cycloset Safety Trial – Clinical Study Report [CSR]), and 29 (The Complete Response to FDA approvable letter to Cycloset for type 2 diabetes) to NDA 20-866: Cycloset™ (Bromocriptine Mesylate) for the treatment of type 2 diabetes submitted on December 12, 2007, March 7, 2008, and April 13, 2008, respectively. This Amendment 30 submission provides the FDA-requested re-formatted efficacy data sets for the Clinical Study Report previously submitted in Amendment 27, contained in Amendment 28 and Summarized in Amendment 29. Subsequent to a teleconference discussion with Dr. Pian of FDA, our statistician for the Cycloset Safety Trial (Study 165-AD-04-03-US-1), [1] _____, and myself held on June 5, 2008, we have prepared "datasets specifically tailored for efficacy" respecting Study 165-AD-04-03-US-1, as Dr. Pian has requested and provide them on data disc with this submission. b(4)

This submission contains 1 CD data disc containing a) the efficacy datasets from the CSR Report Number165-AD-04-03-US-1 in format requested by Dr. Pian, b) a brief overview of HbA1c efficacy analyses from the Cycloset Safety Trial (Study No. 165-AD-04-03-US-1), and c) copies of efficacy data tables from the CSR for reference. This CD has been scanned and found to be virus-free using Symantec AntiVirus Program: 10.1.0.394 Scan Engine: 81.1.0.13 Virus Definition File 06/24/2008 rev. 3 software.

Form 365h follows this letter. If you have any questions regarding this submission, please feel free to contact me at 617 966 8413 or email me at: Anthony_Cincotta@VeroScience.com

Sincerely,

Anthony H. Cincotta

Anthony Cincotta, PhD
President and Chief Scientific Officer

DSI CONSULT: Request for Clinical Inspections

Date:	June 10, 2008
To:	Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46 Joe Salewski., Branch Chief (Acting), GCP2, HFD-47 Name of DSI Primary Reviewer
Through:	Robert Misbin, M.D., Review Division/HFD-510 Hylton Joffe, M.D. Teamleader, Review Division/HFD-510 Mary Parks, M.D., Division Director, DMEP
From:	Jena Weber, Regulatory Health Project Manager/Division/HFD-510
Subject:	**Request for Clinical Site Inspections**

NOTE: updated per DFS 5/13/08

I. General Information

Application: NDA 20-866
Sponsor: VeroScience, Anthony Cincotta, Ph.D., President, CSO 401-816-0525
Drug: Cycloset (bromocriptine mesylate) Tablets
NME: No
Standard (6-month clock)
Pediatric exclusivity: No

PDUFA: October 15, 2008
Action: October 15, 2008
Inspection Summary Goal Date: October 1, 2008

II. Background Information

Include a brief introduction about the application and include the following:

- *New application (re-submission)*
- *Proposed indication: Type 2 Diabetes Mellitus*
- *Brief information*
  - *on drug*
  - *disease*
  - *pivotal studies (large clinical trial, Study 165-AD-04-03-US-1)*

Protocol/Site Identification

Include the Protocol Title/# for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
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Site 215, Charles Herring, M.D. New Hanover Medical Research, 1907 Tradd Court, Wilmington, NC 28410	165-AD-04-03-US-1	157	Type 2 Diabetes Mellitus
Site 260, Thomas Littlejohn, M.D., Piedmont Medical Research, 1901 S. Hawthorne Road, Suite 306, Winston-Salem, NC 27103	165-AD-04-03-US-1	152	Type 2 Diabetes Mellitus
Site 350, Sherwyn Schwartz, M.D., DGD Research Inc. 5107 Medical Drive San Antonio, TX 78229	165-AD-04-03-US-1	183	Type 2 Diabetes Mellitus
Site 537, Elena Barengolts, M.D., Chicago Westside VAMC, CHCS Westside, 820 S. Damien Ave., M/C111, Chicago, IL 60654	165-AD-04-03-US-1	136	Type 2 Diabetes Mellitus

III. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Things to consider in decision to submit request for DSI Audit

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- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*

- *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
- *Expected commonly reported AEs are not reported in the NDA*

- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

Rationale for DSI Audits

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

Domestic Inspections:

Reasons for inspections (please check all that apply):

X___ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
X___ **Other: Please evaluate 3 out of the 5 investigators specified.**

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact *Name of RPM* at Ph: *301-796-xxxx or Name of Medical Officer* at Ph: 301-796-XXXX.

Concurrence: (as needed)

_____ Medical Team Leader
_____ Medical Reviewer
_____ Director, Division Director (for foreign inspection requests only)

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

/s/

Robert Misbin
6/12/2008 02:53:18 PM
MEDICAL OFFICER

Hylton Joffe
6/12/2008 04:21:31 PM
MEDICAL OFFICER

Mary Parks
6/13/2008 02:31:00 PM
MEDICAL OFFICER

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: June 5, 2008

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: Mary Parks, M.D.
Director, Review Division, HFD-510

FROM: Jena Weber, Regulatory Health Project Manager, HFD-510

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 20-866
Cycloset (bromocriptine mesylate) Tablets

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
BON-P6-262	Algorithme Pharma Inc 1200 Beaumont Ave. Mount-Royal, Quebec, Canada H3P 3P1 514-858-6077 Investigator: Eric Sicard, M.D.	[redacted]

b(4)

International Inspections:

(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)

We have requested an international inspection because:

__X__ There is a lack of domestic data that solely supports approval;

_____ Other (please explain):

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **September 30, 2008**. We intend to issue an action letter on this application by **October 15, 2008**. This NDA is a resubmission (response to our AE letter dated October 15, 1999), and is on a 6-month review clock.

Should you require any additional information, please contact Ms. Jena Weber at 301-796-1306.

Contact for VeroScience is:
Anthony Cincotta, Ph.D.
1334 Main Road
Tiverton, RI 02878
401-816-0525

Concurrence:
Hylton Joffe, M.D. Medical Team Leader

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

/s/

Mary Parks
6/6/2008 05:47:31 PM

Weber, Jena M

From: Vaidyanathan, Jayabharathi
'nt: Thursday, June 05, 2008 7:37 AM
: Weber, Jena M
ɔubject: RE: Cycloset

Jena,

Please see the information below:

Study Number	BON-P6-262
Study Title	Single Dose Crossover Comparative Bioavailability Study of Bromocriptine Mesylate 0.8 mg Tablets Following Administration of a 4.8 mg Dose in Healthy Male and Female Volunteers / Fed State
Clinical Site (Name, Address, Phone #)	Algorithme Pharma Inc., 1200 Beaumont Ave., Mount-Royal, Quebec, Canada, H3P 3P1. Telephone: (514) 858-6077
Principal Investigator	Eric Sicard, M.D.
Dosing Dates	Group A Period 1: 2007/08/14 Period 2: 2007/08/21 Group B Period 1: 2007/08/23 Period 2: 2007/08/30
Analytical Site (Name, Address, Phone #)	[redacted]
Analysis Dates	08-Nov-2007 to 11-Dec-2007
Analytical Director	[redacted]
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	120 days

b(4)

Can you also please ask the sponsor the location for the bioanalytical method and validation report?

Thanks,

Jaya

From: Weber, Jena M
Sent: Thursday, June 05, 2008 7:20 AM
To: Vaidyanathan, Jayabharathi
Subject: RE: Cycloset

/a,

Do you have a contact person at the Canada & [redacted] facilities? b(4)

Weber, Jena M

From: Vaidyanathan, Jayabharathi
Sent: Wednesday, June 04, 2008 1:43 PM
To: Weber, Jena M
Cc: Choe, Sally
Subject: Cycloset

NEED TO Consult to DSI

Jena,

Please ask the sponsor:

- Please submit the SAS transport files (or if submitted indicate where the files are located) for the BE study BON-P6-262 data. REQUESTED

DSI requested for:

- DSI inspection is requested for the BE study BON-P6-262. The site details are as follows:

  Clinical facility:
  Algorithme Pharma Inc.
  1200 Beaumont Ave.
  Mount Royal, Quebec, Canada
  H3P 3P1

  Analytical site:

  b(4)

Thanks,

Jaya

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
OSE
tt. Cheryl Campbell

FROM: DMEP
Jena Weber, PM

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
5/20/08		20-866	Labeling (PI, PPI, carton & container)	4/13/08

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Bromocriptine mesylate	S	Anti-diabetic	8/15/08

NAME OF FIRM: VeroScience, LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Labeling re-submission

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- ☐ TYPE A OR B NDA REVIEW
- ☐ END OF PHASE II MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **Approvable letter for this NDA issued on 10/15/1999. Re-submission dated April 13, 2008. Please review and comment prn on all proposed LBL. Each section (PI, PPI, carton & container) is available via EDR. UFGD is October 15, 2008.**

NAME AND PHONE NUMBER OF REQUESTER
Jena Weber, 301-796-1306

METHOD OF DELIVERY (Check one)
☒ DFS ONLY X HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

✓

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

/s/

Jena Weber
5/20/2008 02:08:48 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
OSE
tt. Cheryl Campbell

FROM: DMEP
Jena Weber, PM

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
5/20/08		20-866	Tradename Proposal	4/13/08

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Bromocriptine mesylate	S	Anti-diabetic	**8/15/08**

NAME OF FIRM: VeroScience, LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY REVIEW
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER (SPECIFY BELOW):
☐ OTHER (SPECIFY BELOW):	

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
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- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **Approvable letter for this NDA issued on 10/15/1999.** At this time, the tradename "Cycloset," was **acceptable. Please evaluate again; the UFGD is October 15, 2008.** All labeling is available via EDR under April 13, 2008, resubmission.

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
Jena Weber, 301-796-1306	☒ DFS ONLY X HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Jena Weber
5/20/2008 02:04:06 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-866

NDA ACKNOWLEDGMENT

VeroScience, LLC
Attention: Anthony H. Cincotta, Ph.D.
President and CSO
1334 Main Road
Tiverton, RI 02878

Dear Dr. Cincotta:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Cycloset (bromocriptine mesylate) 0.8 mg Tablets

Date of Application: April 13, 2008

Date of Receipt: April 15, 2008

Our Reference Number: NDA 20-866

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 15, 2008, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism & Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, please call me at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Jena M. Weber
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Jena Weber
5/5/2008 01:06:52 PM

VeroScience, LLC

1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

ORIGINAL

April 13, 2008

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oak Campus
Room 1400 - Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

RECEIVED
APR 15 2008
CDER CDR

Attention: Ms. Jena Weber
Project Manager

N_000-BZ

Re: NDA 20-866, Amendment 29 –Complete Response to FDA approvable letter
Cycloset™ (bromocriptine mesylate) for type 2 diabetes
[Paper and Electronic Submission]

ORIGINAL AMENDMENT
N/A

Dear Dr. Parks,

With this submission, VeroScience LLC (VeroScience) is filing a Complete Response to the Agency's approvable letter for this NDA 20-866, dated October 15, 1999. This NDA was originally filed by the first sponsor, ErgoScience Corp. (Ergo) on August 18, 1997. The Agency issued an approvable letter to the NDA with the major requirement for approval being to conduct a large, simple safety study of Cycloset™ in subjects with type 2 diabetes. Ergo transferred the NDA to PLIVA d.d. (PLIVA) of Zagreb, Croatia in November of 2003. PLIVA then met with the Agency in May 2004 to further the FDA discussions begun with Ergo respecting the study design of the Cycloset™ safety trial. VeroScience collaborated with PLIVA on the study design and execution and the safety trial was initiated in July of 2004. PLIVA then transferred ownership of the NDA to VeroScience in May of 2006 and VeroScience completed the trial (last subject out) in January of 2007 and unblinded the dataset for the trial on May 25 of 2007.

By agreement with Division staff, the large safety trial report (Study No. 165-AD-04-03-US-1) was submitted on December 12, 2007 as Amendment 27 to the NDA and the datasets for this study were filed as amendment 28 in March of 2008. All other issues listed in the approvable letter are addressed in this submission, including a systematic update from the literature, World Health Organization and FDA MedWatch databases of safety data respecting bromocriptine (the active agent in Cycloset™) use over the last 30 years.

In addition to addressing all the requirements from the approvable letter, other changes have taken place over the development period, which necessitate the filing of additional information in this submission. These issues were addressed with the Agency at a Type B meeting held on February 21, 2007 and are as follows.

Section 4 of the pending NDA is updated to provide for Patheon as the manufacturer of commercial product after approval. Ergo utilized Geneva Pharmaceuticals Inc. of Broomfield, CO to manufacture the Cycloset™ product for the clinical studies that were submitted in the originally filed NDA 20-866. Upon transfer of Ergo ownership of the NDA to PLIVA in November, 2003, PLIVA became the new manufacturer of Cycloset™ for subsequent clinical studies, including the large safety trial (Study No. 165-AD-04-03-US-1) and manufacturing was

Results for the primary endpoint are displayed in table 14.2.1.1. With the 2:1 randomization, 176 Cycloset™ and 98 placebo subjects experienced a SAE, yielding a rate ratio of 0.88 and a hazard ratio of all cause SAE of 1.023 (96% one sided confidence limit of 1.27). For the secondary endpoint, composite cardiovascular SAEs, 31 events were confirmed by adjudication for the Cycloset™ group (1.5%) and 31 events were confirmed for the placebo group (3.0%), yielding a rate ratio of 0.5 and a hazard ratio of 0.566 with a 96% one-sided confidence limit of 0.88. As can be seen from table 14.2.2.1, incidence rate for each component of the cardiovascular composite was reduced in the Cycloset™ treated patients. Finally, following 6 months on study drug, subjects receiving Cycloset™ treatment (n= 121) experienced an HbA1c reduction of -0.674 from baseline versus an increase for placebo-treated subjects (n = 71) of 0.015 to give a placebo-adjusted change from baseline of -0.69 (P <0.0001). Of these Cycloset treated subjects, 39% (vs. 11% placebo) reached the ADA goal of HbA1c of ≤ 7.0 (P<0.0007) and 53% (vs. 21% placebo) experienced a minimum reduction in HbA1c from baseline of 0.7 (p<0.0001).

We recognize that these cardiovascular safety outcomes from a "real-world" study design are particularly important in the context of the chronic and progressive nature of T2DM. It is of note that these controlled trial results are very consistent with the cardiovascular-related findings of a case cohort controlled analysis of the UK GPRD database, which was previously submitted to the NDA.

We will move quickly to finalize the safety study report and amend the NDA. We thank you for the contributions that you and your colleagues have made to designing and analyzing this study. We look forward to your continued assistance as offered at our last Type B meeting in February of this year. If there are any questions regarding this information, please feel free to contact me at 617 966 8413 or email me at Anthony_Cincotta@VeroScience.com.

cell

Sincerely,

Anthony H. Cincotta

Anthony H. Cincotta, Ph.D.
President and Chief Science Officer

CC:
Robert Misbin, M.D.
Jena Weber

Rec. 6/4/07

VeroScience, LLC

1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

June 1, 2007

Mary Parks, M.D.
Director, Division of Metabolic and Endocrinology Products (DMEP)
Food and Drug Administration
White Oaks Campus
Room 1400 Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20903-0002

Attention: Ms. Jena Weber
Project Manager

Re: NDA 20-866: Cycloset™ (Bromocriptine Mesylate)
Notification of Safety Trial Completion and Results

Dear Dr. Parks,

Reference is made to our NDA 20-866: Cycloset for the Treatment of Type 2 Diabetes Mellitus.

In follow up to the very productive meeting that VeroScience held with the Agency on February 21, 2007 and as a courtesy to the Division, we wish to communicate important information to you before any other external distribution occurs. We have completed and unblinded our large safety trial of Cycloset in subjects with Type 2 diabetes. After reviewing the immediately available data, we have concluded that the results are likely to prompt substantial interest among the expert community. We are therefore enclosing tables of data for the primary and secondary safety endpoints as well as for the efficacy of Cycloset in the pre-specified metformin plus sulfonylurea-treated subpopulation. These results have not been communicated beyond our organization. We are committed to providing the finalized data set and study report to the Agency as soon as possible, and in every way, supporting the Agency's review of this trial.

This safety trial was a 52-week, double blind, placebo-controlled, multicenter study in patients receiving a diabetes therapeutic regimen consisting of either a) diet, or b) no more than two hypoglycemic agents, or c) insulin with or without one additional oral agent that were randomized to treatment with either Cycloset™ (titrated to maximal tolerated dose of 1.6 mg to no greater than 4.8 mg daily) (n= 2,054), or placebo (n= 1,016). The primary and secondary endpoints were time to first all-cause serious adverse event (SAE) and cardiovascular SAE (defined as composite of myocardial infarction, stroke, coronary revascularization, or hospitalization for angina or congestive heart failure), respectively, which were adjudicated by an independent review committee under a defined charter, previously submitted to the Agency. This trial design set a predefined margin of non-inferiority for the primary and secondary endpoints as a hazard ratio of Cycloset™ to Placebo of 1.5. Per the Statistical Analysis Plan for the trial, an analysis of the between-treatment differences in change from baseline to week 24 in HbA1c among subjects receiving metformin and sulfonylurea and HbA1c of ≥ 7.5 but < 10.0 at baseline was also performed.

1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

performed at their facility in Zagreb, Croatia. When PLIVA transferred ownership of the NDA to VeroScience in May of 2006 PLIVA no longer had interest in manufacturing Cycloset™. Consequently, VeroScience contracted with a new contract manufacturer, Patheon Inc. of Cincinnati, Ohio, to produce product for commercial distribution upon NDA approval. We are updating the CMC section to provide for Patheon as the manufacturer of drug product. Full details of the manufacturing and controls for the manufacture of drug product by Patheon are included in this submission.

Section 6 of the pending NDA requires updating to demonstrate bioequivalence of the to-be marketed product from Patheon to the product utilized within the clinical studies of the NDA. Again, at the Type B meeting this issue of bridging the data obtained within the NDA with the to-be marketed product from Patheon was discussed. Agreement was reached to perform a bioequivalence study to bridge the product manufactured by Patheon for marketing to the product manufactured by PLIVA and utilized in the large Cycloset™ safety trial. The bioequivalence study report (Study No. BON-P6-262) is included in this submission and we trust that the Agency will agree that the two formulations are bioequivalent.

In addition to this bioequivalence study, a bridge was needed to the original NDA data that was generated using product manufactured by Geneva Pharmaceuticals Inc. (Geneva) of Broomfield, CO in 1997. This Geneva product is no longer available and as such, at the Type B meeting agreement was reached to provide a clinical efficacy bridge using efficacy data from pre-specified efficacy subgroups within the Statistical Analysis Plan for the large safety trial (165-AD-04-03-US-1) to efficacy data from Phase 3 studies within the original NDA. The clinical bridge data are included in this submission in Section 6 and we believe you will find that the data support the consistency of efficacy response to Cycloset™ regardless of manufacturer.

As noted in the Type B meeting package and as discussed at the meeting, this complete response to the approvable letter is formatted in the same manner as the original NDA. All relevant sections are updated as necessary based on new ownership, new manufacturing and new data. This Amendment updates Sections 2, 3, 4, 5, 6, 8, 9, and 10. An Index is provided in Section 1. As agreed with the Agency, case report forms from all studies in the amendment, pharmacovigilance datasets, cited literature, and additional copies of the package insert are included on DVDs in an effort to markedly limit the number of paper volumes to this submission. These electronic data are all contained within Volume 2 of the Blue Archival Binder. These DVDs have been scanned and found to be virus-free using Symantec AntiVirus Program: 10.1.0.394 Scan Engine: 71.4.0.15 Virus Definition File: 04/13/08 rev. 3 software. Each technical review section contains a copy of Volume 1 of this submission including the Index, Draft Labeling and the Amendment Summary. The Amendment Summary contains a revised annotated package insert.

We have worked in earnest to follow the guidance and advice from the Division of Metabolic and Endocrinology Products, in the completion of this submission. VeroScience wishes to thank the Division for its attention, cooperation and guidance in this process. Should you have any questions or require any additional information regarding this submission, please feel free to contact the undersigned at (phone) 617 966 8413, (fax) 401 608 3079, or (email) Anthony_Cincotta@VeroScience.com.

Sincerely,

Anthony H. Cincotta

Anthony H. Cincotta, PhD
President and Chief Scientific Officer

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT VeroScience, LLC	DATE OF SUBMISSION 04/13/2008
TELEPHONE NO. *(Include Area Code)* 401-816-0525	FACSIMILE *(FAX)* Number *(Include Area Code)* 401-816-0524
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 1334 Main Road, Tiverton, RI 02878	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

RECEIVED
APR 15 2008
CDER CDR

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 20-866

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* bromocriptine mesylate	PROPRIETARY NAME *(trade name)* IF ANY Cycloset

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* (5'α)-2-Bromo-12'-hydroxy-2'-(1-methylethyl)-5'-(2-methylpropyl)ergotaman-3',6',18-trione	CODE NAME *(If any)*

DOSAGE FORM: tablet	STRENGTHS: 0.8 mg	ROUTE OF ADMINISTRATION: oral

(PROPOSED) INDICATION(S) FOR USE:
Treatment of Type 2 Diabetes Mellitus

PLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☒ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Complete Response to Approvable Letter for NDA 20-866

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 37 THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

ɔse References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 34,661

This application contains the following items: *(Check all that apply)*	
☒	1. Index
☒	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☒	3. Summary (21 CFR 314.50 (c))
☒	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☒	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☒	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☒	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☒	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☒	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☒	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☒	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☒	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☒	16. Debarment certification (FD&C Act 306 (k)(1))
☒	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☒	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Anthony H. Cincotta	Anthony H. Cincotta, Ph.D., President and CSO	04/13/2008

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
1334 Main Road, Tiverton, RI 02878	(401) 816-0525

Public reporting burden for this collection of information is estimated to average 24 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:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

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 & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-866

VeroScience, LLC
Attention: Anthony H. Cincotta, Ph.D.
President and Chief Science Officer
1334 Main Road
Tiverton, RI 02878

Dear Dr. Cincotta:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cycloset™ (bromocriptine mesylate) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on February 21, 2007.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

VeroScience, LLC
1334 Main Road, Tiverton, RI 02878
(P): 401-816-0525 (F) 401-816-0524

I certify that the Field Copy of Amendment 29 to NDA 20-866 for Cycloset™ bromocriptine mesylate is an exact duplicate of Section 4 - Chemistry, Manufacturing and Controls as filed in the NDA Amendment.

Anthony H. Cincotta

Anthony H. Cincotta, Ph. D.
President

April 13, 2008
Date

INDUSTRY MEETING MINUTES

MEETING TYPE:	B
MEETING CATEGORY:	Response to Approvable letter
INTERNAL MEETING DATE:	Friday February 2, 2007
INDUSTRY MEETING DATE:	Wednesday February 21, 2007
APPLICATION NUMBER:	NDA 20-866
PRODUCT NAME:	Cycloset (bromocriptine mesylate)
SPONSOR:	VeroScience
MEETING CHAIR:	Mary Parks, M.D., Director, Division of Metabolism & Endocrinology Products (DMEP)
MEETING RECORDER:	Jena Weber, Project Manager

Division of Metabolism and Endocrinology Products (DMEP)

Mary Parks, M.D.	Division Director
Robert Misbin, M.D.	Clinical Reviewer
Jena Weber, BS	Project Manager

Office of Biometrics II, HFD-715

Todd Sahlroot, Ph.D.	Team Leader - Biometrics
Lee-Ping Pian, Ph.D.	Biometrics Reviewer

Office of Clinical Pharmacology (OCP)

Qiu Wei, Ph.D.	OCP Reviewer
Jim Wei, M.D., Ph.D.	OCP Reviewer

VeroScience

Anthony Cincotta, Ph.D.	President, Chief Science Officer
Richard Scranton, M.D., MPH	Chief Medical Officer
[redacted]	[redacted]
Michael Gaziano, M.D., MPH	Brigham & Women's Hospital, Principal Investigator
David Adams, Esq.	Venable LLP

b(4)

b(4)

Regulatory Background

VeroScience has completed the acquisition of Cycloset (bromocriptine mesylate) from the former sponsor, PLIVA, d.d. (PLIVA). Notifications of the transfer of ownership for NDA 20-866 were submitted to the Agency in accordance with 21 CFR 3 14.72, and notifications were acknowledged by the Agency on June 22, 2006.

An approvable letter for NDA 20-866 was issued to Ergo Science Corp. (Ergo) by FDA on October 15, 1999. The approvable letter included a series of comments arising from the Agency's review. The Agency held a meeting with Ergo on April 6, 2000, to discuss appropriate strategies to obtain NDA approval.

Trial Commitment
The Agency's principal recommendation for approval was that the sponsor (Ergo) should perform a large, "simple" clinical trial (SCT) to show that bromocriptine treatment does not increase the risk of serious cardiovascular events in patients with T2DM. VeroScience is now completing the agreed SCT to address the aforementioned safety concern. A planned interim analysis of the primary and secondary endpoints of the trial, including cardiovascular safety, was conducted in July 2006, and the trial's last patient will finish therapy on December 27, 2006.

Meeting Purpose:
a) review the Cycloset amended NDA 20,866 filing plans of the new sponsor, VeroScience and b) confirm that the Agency requirements for filing a complete and final response to the approvable letter and requests of the May 11,2004, meeting will have been met by following the Sponsor's plans for filing, c) brief discussion regarding the manufacture of Cycloset by a U.S. manufacturer, Patheon Inc. VeroScience seeks the Agency's concurrence with VeroScience's plan to utilize this manufacturer for submission of the registration batches with the final response amendment to the NDA and to use this supplier for commercialization of the Cycloset product. VeroScience has just submitted protocols and an overall proposal for linking the versions of the drug product used in the clinical trials with the product to be marketed.

Objectives and Expected Outcomes
1. Provide status of current ongoing clinical safety trial (last subject out of study on December 27, 2006), and discuss timeline for submission of approvable letter response.
2. Receive any further comments regarding the proposed plan for bioequivalence (bridging) studies of clinical studies supply and commercial product.
3. Achieve FDA acceptance of the finalized Statistical Analysis Plan for the ongoing clinical safety trial to now include secondary efficacy outcomes.
4. Receive FDA acceptance of sponsor's plans for new manufacturing site for registration batches of cycloset and commercial product focusing on stability data available at the time of filing.
5. Receive FDA acceptance of plan for filing a final response to the AE letter.

Proposed Indications:
The proposed indications for Cycloset (bromocriptine mesylate) are:
(a) As monotherapy to lower blood glucose in patients with type 2 diabetes mellitus whose hyperglycemia is inadequately controlled with diet and exercise;
(b) For use in combination therapy with a sulfonylurea and/or metformin to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise plus therapy with any of the following agents: metformin, sulfonylurea, or bromocriptine.

Note: VeroScience was in agreement with the Agency's internal response to questions 1, 3, 4, and 6. Meeting discussion was mostly central to questions 2 and 5.

Questions

1. In addressing the sole deficiency of the NDA approvable letter of October 15, 1999, the sponsors of NDA 20-866, conferred with FDA to design a large, "simple" safety trial of Cycloset (bromocriptine mesylate). Agreement was reached on the design of the trial at the May 11, 2004, meeting between representatives of PLIVA and FDA. The protocol was finalized and submitted to the FDA on June 25, 2004, (TND Serial No.0200). VeroScience has finalized the Statistical Analysis Plan (SAP) for the safety trial, which is submitted within the briefing document for this meeting request, for FDA review and concurrence. VeroScience has concluded that this analysis plan will support a robust determination of the safety study objectives that will allow the remaining deficiency to be resolved. Does FDA agree?
FDA Response: As requested in the meeting minutes on April 6, 2000, 'Near complete follow-up will be critical with ascertainment of vital and critical status, including as myocardial infarction (MI's), stroke and death.' The submission should include documentation of all events including events following a time-to-event endpoint and events occurring following discontinuation of study drug.

Analyses of primary and secondary endpoints are time to event analyses of the hazard ratio between Cycloset and placebo. As a sensitivity analysis, incidence rates should be compared between Cycloset and placebo using risk ratios.
<u>From 2/21/07 meeting:</u> VeroScience acknowledged that a sensitivity analysis will be provided.

2. In the approvable letter of October 15, 1999, of NDA 20-866, the Agency requested that the sponsor update the NDA with current safety information on the new drug. VeroScience plans to do so, in part, by providing such information from World Health Organization, U.S. Food and Drug Administration, published literature and pharmaceutical pharmacovigilance databases on this topic. Also, VeroScience will provide available data from analyses of a large prospective, cohort-controlled epidemiological study from the United Kingdom General Practitioners Research Database of myocardial infarction rates in subjects exposed to bromocriptine. Moreover, VeroScience plans to provide comparison tables of safety data from the ongoing large "simple" safety trial versus the safety data currently in the NDA. The comparison table shells are provided in the briefing document. The above data sets will be compiled into an Overall Summary of Safety (separate from and in addition to the safety trial study report) as part of the amendment to the NDA. VeroScience has concluded that this approach satisfies the Agency's request for updating the safety information on Cycloset Does the FDA agree?
FDA Response: The proposal is adequate with respect to the issues raised in the approvable letter. But a new concern, valvulopathy, has emerged and should be addressed. Whether ECHO studies were done or not should be stated; a sub-study including coding on valvulopathy may be required. Patients still taking drug could constitute a population in which to address this issue.
<u>From 2/21/07 meeting, add:</u>

- Bromocryptine – antagonist of the 5-HT_{2B} receptor.
- Previous echo study submitted to IND 34,660 (YY 1999);
  Cycloset 49 subjects, 49 controls for 6 month study showed no valvular abnormalities.
- Kim et al (Movement Disorders, 21, 2006) Echo study;
  22 Bromocryptine, 36 Pergolide (lower dose), 20 age matched control;
  Conclusion – no significant valvular abnormalities.
- Post-marketing surveillance – estimated———person year exposures (France); b(4)
  1 reported case of severe TR (mild MR & AR) with bromocriptine (40 mg – 5 years).

WHO adverse reporting - no cases of valvular heart disease solely attributed to bromocriptine
(1 case of mitral stenosis while taking bromocriptine and pergolide).

The Division stated that these additional data are likely sufficient to address any concerns of valvulopathy associated with bromocriptine use and recommended that they be incorporated in the resubmission to the NDA.

3. Metformin has generally become the preferred first line treatment of T2DM. All other approved oral therapies for T2DM have indications for combination with metformin. Because metformin was not yet approved during the development of bromocriptine mesylate, no clinical trials were performed with metformin. FDA had indicated at the May 11, 2004, meeting with PLIVA that glycemic control - efficacy data of Cycloset in subjects on metformin would be helpful in labeling of the drug. The availability of a large cohort of subjects on the combination of metformin plus sulfonylurea and Cycloset in the safety trial could provide data to support information on efficacy as well as safety of this combination.

VeroScience has specified in the final SAP provisions for the analysis of efficacy data from the cohort on metformin plus sulfonylurea and cycloset. This plan is submitted within the briefing document for this meeting request for FDA review and concurrence. VeroScience has concluded that these data, so analyzed, would provide information of cycloset efficacy as well as safety in a population of subjects treated with metformin. Does FDA agree?
FDA Response: This will be a review issue; language to the appropriate section(s) of the PI will reflect the analysis of submitted data.
<u>From 2/21/07 meeting:</u> the SAP appears acceptable on face-value. However, the submission must contain clean efficacy data. In addition to previously complied/submitted data, a robust study to support bridging, could prove to be clinically beneficial as a link supporting efficacy (a new trial using metformin could be considered). Also see response to question 5.

4. In its October 15, 1999 approvable letter, FDA provided a short list of questions related to manufacturing of the [redacted] and a scored 0.8 mg tablet dosage form. VeroScience will not be pursuing or seeking approval for manufacturing and commercialization of either the [redacted] 0.8 mg tablet dosage forms in its current amended NDA filing. VeroScience has concluded that no further responses are necessary to address these particular manufacturing queries from the Agency. Does the FDA Agree? b(4)
FDA Response: Yes.

5. The previous sponsor (Pliva d.d.) was also the manufacturer of the Cycloset product utilized in the ongoing safety trial. However, Pliva d.d. is no longer manufacturing Cycloset. Consequently, VeroScience has contracted with a new U.S. manufacturer for the manufacture of registration batches and commercialization of Cycloset product. As a result of moving the manufacture of Cycloset to a new facility, the amended NDA will compare three different versions of drug product:

- The product used for the original clinical trials in the originally filed NDA
- The product used in the current safety study, and
- The product proposed for marketing.

VeroScience has provided a plan for bridging of bioequivalence among these three versions. These protocols and the overall bridging approach were submitted recently for review under the Cycloset IND (Serial No. 0321). Does the FDA agree with these plans?

FDA Response: We have never granted a pivotal BE assessment based on cross-study comparison. Therefore, the proposed bioequivalence study to demonstrate BE between the products used in original NDA submission and the products used in the ongoing safety trial is not acceptable. Pivotal bioequivalence needs to be established in a single study. If the products used in the pivotal clinical trials in the original NDA are no longer available, a clinical efficacy bridge study is recommended.

<u>From 2/21/07 meeting:</u> the company stated that a non-traditional approach was taken to assess BE of this product due to the 3 different sponsors and 3 different manufacturing sites. The current manufacturing contractor is Patheon Inc. (Cincinnati, OH), and provides for the same ingredients, formulations, chemical features, etc. The company provided a dissolution profile of tablets from three manufacturing sites. A BE trial of the PLIVA product versus the Patheon product will be conducted.

FDA emphasized that the dissolution profile for Geneva site was from historic data. Such dissolution analysis for f2 calculation across studies is not valid. The site change is considered a Level 3, which requires an in-vivo BE study. The originally proposed BE study only can be used as supportive.

This method of bridging between formulations is not acceptable. While the Division recognizes that there is no other alternative since the initial drug product is no longer available, the company must provide sufficient evidence supporting efficacy of the to-be-marketed formulation. There was extensive discussion surrounding efficacy analyses from the cardiac safety study. The medical and statistical reviewers expressed concern that confounding effects of background therapy or study design will not permit a reliable estimate of efficacy. We can not commit that this proposal is adequate for establishing efficacy and it will therefore be a review issue. Alternatively, the company can conduct an efficacy study evaluating the effect of Cycloset in combination with metformin. As there is a high likelihood that these two drugs would be used together in practice, a well-designed study to evaluate efficacy (and safety) may overcome the problems of bridging efficacy through indirect bioequivalence studies and analysis of your safety study.

6. VeroScience is moving the manufacture of Cycloset to a new facility, Patheon Inc., in Cincinnati, Ohio. VeroScience will provide information and the plan for the transfer of manufacturing to this facility as well as for the stability testing of NDA and commercial drug products in an upcoming IND submission on CMC in January. VeroScience will also be providing information on the stability data available at the time of the anticipated NDA amendment submission. Does the FDA agree with these plans?
FDA Response: Yes, we agree with this proposal.

7. VeroScience intends to file a final response to the Agency approvable letter for NDA 20-866 in the second quarter of 2007. It will consist of the results of the large "simple" safety trial (both safety and efficacy as detailed in the study SAP), summaries of NDA safety and efficacy data (including study reports from those trials not completed at the time of the original NDA filing), a world-wide database compilation on clinical safety of bromocriptine, the complete responses to all approvable letter queries, as well as the information and data to support the new manufacturing facility and the commercial drug product, and revised labeling for the drug product. VeroScience has concluded that these data and information will address all deficiencies and questions raised by the Agency so that the review of NDA 20-866 may be completed. Does the FDA agree?

FDA Response: This will be a review issue.

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/s/

Jena Weber
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-866

VeroScience LLC
Attention: Anthony H. Cincotta, Ph.D.
1334 Main Road
Tiverton, RI 02878

Dear Dr. Cincotta:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for Cycloset (bromocriptine mesylate).

We also refer to your December 21, 2006, correspondence, received December 22, 2006, requesting a meeting to discuss your final response to our approvable letter dated October 15, 1999.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: Tuesday February 13, 2007
Time: 3:30 – 5:00 pm
Location: White Oak Campus, Building 22
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Tentative CDER participants:

Blair Fraser, Ph.D.	Branch Chief, Chemistry
Robert Meyer, M.D.	Office Director (ODE-II)
Robert Misbin, M.D.	Clinical Reviewer
Stephen Moore, Ph.D.	Chemistry
Mary Parks, M.D.	Division Director (DMEP)
Lee-Ping Pian, Ph.D.	Biometrics
Curt Rosebraugh, M.D.	Deputy Office Director (ODE-II)
Todd Sahlroot, Ph.D.	Team Leader – Biometrics
Wei Qiu, Ph.D.	Biopharmaceutics Reviewer
Jena Weber, BS	Project Manager
Jim Wei, M.D., Ph.D.	Acting Team Leader, Biopharmaceutics

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at Jena.Weber@fda.hhs.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards my number (301-796-1306) to request an escort to the conference room.

If you have any questions, please call me at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Jena Weber
1/5/2007 04:20:12 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-866

VeroScience LLC
Attention: Anthony Cincotta, Ph.D.
1334 Main Road
Tiverton, RI 02878

Dear Dr. Cincotta:

We acknowledge receipt on May 18, 2006, of your May 16, 2006, correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug application (NDA):

Name of Drug Product:	Cycloset™ (bromocriptine mesylate) Tablets
NDA Number:	20-866
Name of New Applicant:	VeroScience LLC
Name of Previous Applicant:	Pliva Inc.

Your correspondence provided the information necessary to effect this change, and we have revised our records to indicate VeroScience LLC as the sponsor of record for this application

All changes in the NDA from those described by the original owner, such as manufacturing facilities and controls, must be reported to us prior to implementation. Refer to the *Guidance for Industry: Changes to an Approved NDA or ANDA* for information on reporting requirements. We request that you notify your suppliers and contractors who have DMFs referenced by your application of the change in ownership so that they can submit a new letter of authorization (LOA) to their Drug Master File(s).

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81. In addition, you are responsible for any correspondence outstanding as of the effective date of the transfer.

Please cite the NDA number listed above at the top of the first page of all submissions to this application.

Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call me at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Pliva Inc.
72 Eagle Rock Avenue; P.O. Box 371
East Hanover, NJ 07936

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/s/

Jena Weber
6/22/2006 08:35:11 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-866

Attention: b(4)

b(4)

Dear Mr.

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cycloset (bromocriptine mesylate) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on May 11, 2004. The purpose of this meeting was to discuss the Agency's recommendation that a large, simple clinical trial be conducted in order to address concerns of a possible increase in myocardial infarction (MI) occurring in patients receiving bromocriptine.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at 301-827-6411.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	Tuesday May 11, 2004
TIME:	9:30 pm
LOCATION:	17-05
APPLICATION:	NDA 20-866
TYPE OF MEETING:	Type A
MEETING CHAIR:	David Orloff, M.D., Division Director, Metabolic and Endocrine Drug Products (DMEDP), HFD-510
MEETING RECORDER:	Jena Weber, Project Manager

Division of Metabolic and Endocrine Drug Products (DMEDP), HFD-510:

David Orloff, M.D.	Division Director
Robert Misbin, M.D.	Clinical Reviewer
Bruce Stadel, M.D.	Clinical Reviewer
Jena Weber, BS	Project Manager
Kati Johnson, R.Ph.	Chief, Project Management Staff

Office of Biometrics II, HFD-715

Todd Sahlroot, Ph.D.	Team Leader – Biometrics
Lee-Ping Pian, Ph.D.	Biometrics Reviewer

PLIVA:

Lidija Brnic, M.D.	Regulatory Affairs
Donald Waters, Ph.D.	Clinical Research
Janet Peterson, Ph.D.	Clinical Research
Marko Kolega, M.D.	Project Director
Anthony Cincotta, Ph.D.	Consultant
Marcia Testa, M.D., Ph.D.	Consultant – Harvard Medical School
Donald Simonson, M.D.	Principal Investigator

b(4)

Proposed Indication: As an adjunct to diet and exercise to lower blood glucose in patients with type 2 diabetes mellitus.

Purpose of the Meeting: To obtain feedback on the design of the proposed clinical study to evaluate the potential for significant increase in the risk of serious cardiac adverse events in patients receiving bromocriptine; analyses and/or additional data needed to establish CV safety of bromocriptine; miscellaneous Agency advice in pursuing NDA approval for this product.

Background: NDA 20-866 was initially submitted on August 18, 1997. A **not approvable** letter citing deficiencies of efficacy and safety (particularly possible adverse cardiac effects) was issued on November 20, 1998. The company provided a complete response to this letter on April 15, 1999. An **approvable** letter was issued by the Agency on October 15, 1999. Deficiencies in the clinical, biopharmaceutics, and pharmacology and toxicology sections of the application were cited.

1. Based on the Agency's feedback as summarized in the approvable letter to NDA 20-866 dated October 15, 1999, and as expressed in discussions that occurred during the meeting held on April 6, 2000, it is "PLIVA's understanding" that FDA has agreed that the application for Cycloset® may be approved pending (1) successful completion of and submission of data from a clinical trial to evaluate the potential for a significant increased risk of serious adverse events (including MI, stroke, and death) with Cycloset® treatment and (2) submission of updated safety data and draft labeling along with adequate data to address the biopharmaceutic, pharmacology, and toxicology deficiencies noted in the 1999 approvable letter. Is this assessment of FDA's position accurate?
FDA Response: In general, yes. However, we have specific comments at this time:

   1. **The population enrolled in this trial must be representative of the broad population of subjects who will use this drug; for example, by severity and duration of diabetes and by use of other anti-diabetic medications.**

   2. **A Phase 4 program studying the addition of Cycloset to metformin should be considered. Concomitant usage of insulin and Cycloset is not appropriate.**

   3. **Provide interpretations for the possible outcomes of the proposed non-inferiority trial – in particular, for the outcome where there is evidence of adverse effects, but less than significant according to the prespecified statistical test.**

   4. **Justify the proposed duration of the trial according to the relationship between time since starting bromocriptine and the occurrence of myocardial infarction, stroke, and other cardiovascular events, using randomized trial and observational study data.**

   5. **Justify the proposed inclusion/exclusion criteria in relation to the proposed treatment population, as defined by the proposed labeling.**

   6. **Justify using discontinuation rates rather than event rates for outcomes, or change to event rates, or change to event rates. Vital and clinical status should be ascertained at the closure of the trial.**

   7. **Show the power of the proposed trial for myocardial infarction, and stroke, in addition to the currently proposed outcome.**

   8. **Provide an estimate for the length of time needed to complete the entire study.**

   9. **Provide a stopping rule.**

2. PLIVA believes that the design and size of the proposed clinical trial as outlined in the protocol submitted on March 4, 2004, are appropriate to meet the stated objectives, and that these objectives are appropriate to address the concerns that the Agency has expressed regarding the potential risk of serious adverse events (including MI, stroke, and death) that may be associated with Cycloset® treatment. Does FDA agree?
FDA Response: FDA recommends a 1-year trial with at least 2000 patients treated with Cycloset.

3. PLIVA believes that if the proposed clinical trial has a positive outcome (i.e., the study demonstrates with 90% power that the event rate for Cycloset® is at least as low as the event rate for placebo), the results from this proposed trial, along with the previously submitted data on clinical efficacy and safety, as well as updated labeling and data on safety, biopharmaceutics, pharmacology, and toxicology, should result in approval of NDA 20-866. Does FDA agree?
FDA Response: The non-inferiority margin (1.5) represents an increase of 22 events or equivalently a 50% increase in relative risk. This allowable risk increase may be too liberal. The margin could be tightened by increasing the length of the trial from 6 months to one year. For example, assuming a doubling of incidence rates from 3% to 6% under linearity, 22 events represent a 25% increase in relative risk.

Following additional internal discussion of the appropriate Type I error rate, the analysis should be conducted at a two-sided alpha = 10%.

A futility analysis should be added to the interim analysis plan.

ost meeting comment: The Division concurs with the Sponsor's minutes of the May 11, 2004, meeting submitted to the Agency on May 27, 2004.

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/s/

Jena Weber
6/10/04 09:39:45 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-866

b(4)

Attention:

b(4)

Dear b(4)

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cycloset (bromocriptine mesylate) Tablets.

We also refer to your March 4, 2004, correspondence, received March 5, 2004, requesting a meeting to discuss our recommendation that you conduct a "large, simple clinical trial to address the concern of possible increased myocardial infarction (MI) in patients receiving bromocriptine."

Please note that the date, time and room location for this meeting has been changed to:

Date: Tuesday May 11, 2004
Time: 9:30 AM
Location: Parklawn Building, Room 17-05

Two additional CDER participants have also been added:

Judy Staffa, Ph.D.	Office of Drug Safety (Epidemiology)
Sandra Birdsong	Office of Drug Safety, Project Manager

If you have any questions, please call me at 301-827-6422.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Jena Weber
4/9/04 02:02:34 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: ODS (Room 15B-08, PKLN Bldg.)
Sandra Birdsong, HFD-430/Attn: Judy Staffa, Ph.D., HFD-410

FROM: Jena Weber, HFD-510
(301) 827-6422

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
March 26, 2004		20-866	Clinical Study Protocol	March 4, 2004

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Cycloset (Bromocriptine Mesylate)	High	Type 2 diabetes	April 9, 2004

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY REVIEW
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER (SPECIFY BELOW):
☐ OTHER (SPECIFY BELOW):	

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please evaluate a new Clinical Study Protocol, CYCSS-04, *A Randomized, Double-Blind, Placebo-Controlled Trial to Assess Safety and Tolerability during Treatment of Type 2 Diabetes with Usual Diabetes Therapy and either Cycloset or Placebo.* Information requested by MO for a meeting with the sponsor.
Feel free to speak with Dr. Bruce Stadel, medical officer, regarding this consult @301-827-6417.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
Dr. Mary Parks, Deputy Director, HFD-510	M.A. Simoneau, Reg. PM for Jena Weber
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Mary Parks
3/26/04 09:59:11 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-866

b(4)

Attention:

b(4)

Dear b(4)

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cycloset (bromocriptine mesylate) Tablets.

We also refer to your March 4, 2004, correspondence, received March 5, 2004, requesting a meeting to discuss our recommendation that you conduct a "large, simple clinical trial to address the concern of possible increased myocardial infarction (MI) in patients receiving bromocriptine."

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type "A" meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: Monday April 12, 2004
Time: 10 AM
Location: Parklawn Building, 3rd floor conference room "B"

Tentative CDER participants:

David Orloff, M.D.	Division Director, HFD-510
Robert Misbin, M.D.	Clinical Reviewer
Bruce Stadel, M.D.	Clinical/Epidemiology Reviewer
Todd Sahlroot, Ph.D.	**Team Leader – Biometrics**
Lee-Ping Pian, Ph.D.	Biometrics Reviewer
Jena Weber, BS	Project Manager

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at **Weberj@cder.fda.gov** so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Ms. Jena Weber, 301-827-6422.

Provide the background information for this meeting (three copies to the NDA and 8 desk copies to me) at least one month prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by **March 19, 2004,** we may cancel or reschedule the meeting.

If you have any questions, please call me at 301-827-6422.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Jena Weber
3/11/04 01:16:21 PM

MEMORANDUM

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

DATE: January 5, 2004

TO: Memo to the File

FROM: Lina AlJuburi, Regulatory Health Project Manager; HFD-510

SUBJECT: **Change IND status from terminated to active due to change in sponsorship for IND 34,661 for Bromocriptine Mesylate Tablets and change in sponsorship for IND 34,661 and NDA 20-866**

A report request was sent to the sponsor of this IND, Ergo Science Corporation, on February 6, 2003, to fulfill the requirement for an annual report of progress of the investigation. This letter was returned for an undeliverable address and no other address was on file for this application. Therefore, the application was considered terminated.

On December 15, 2003, a request was received from the new sponsor, PLIVA Inc., with the required information from Ergo Science Corporation to transfer sponsorship of pending NDA 20-866 and IND 34,611 for Bromocryptine Mesylate Tablets.

Because of this updated information, the status of IND 34,661 needs to be changed from terminated to active. PLIVA Pharmaceuticals has been notified in writing of the requirements to submit annual reports and was asked to submit one within 30 days of receiving the letter acknowledging the transfer of sponsorship.

The sponsor information needs to be updated for both IND 34,661 and NDA 20-866 to include:

New Sponsor Information

PLIVA Inc.
72 Eagle Rock Avenue
P.O. Box 371
East Hanover, NJ 07936

Contact Person: Roger Schwede, VP of R&D and Regulatory Affairs
Phone #: 973-599-4352

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/s/

Lina Aljuburi
1/5/04 02:19:06 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-866

Ergo Research Corporation
Attention: David Burt
President and CEO
Jefferson Office Park; 780 Turnpike Street, Suite 205
North Andover, MA 08145

Dear Mr. Burt:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cycloset (bromocryptine) capsules.

Our letter of October 15, 1999, notified you that your application was approvable. We have not received a complete response to this letter. We also refer to the minutes from our meeting of April 6, 2000, in which we stated that any future protocols for studies that you wish to conduct should be submitted to the Agency for our review and comment before these trials commence. We note that you have not submitted any proposed protocols.

If you do not submit a complete response, or withdraw the NDA under 21 CFR 314.65, within 30 days, we will withdraw this application under 21 CFR 314.65. Withdrawal does not prejudice refiling of the application. You may reference the information contained in the withdrawn application in any future submission.

If you have any questions, please call me at 301-827-6422.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Jena Weber
3/18/03 12:50:20 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-866

Ergo Research Corporation
Attention: David Burt, President and CEO
Jefferson Office Park
780 Turnpike Street, Suite 205
North Andover, MA 08145

Dear Mr. Burt:

We received your July 12, 2002, correspondence on July 12, 2002, requesting a meeting to discuss the contents of the approvable letter issued by the Agency on October 15, 1999, and your development plans for this product in order to obtain approval of this NDA. We considered your request and concluded that the meeting is unnecessary. Please reference the minutes from our meeting of April 6, 2000, in which we stated that any future protocols for studies that you wish to conduct should be submitted to the Agency for our review and comment before these trials commence.

If you disagree with our decision, you may discuss the matter with Ms. Jena Weber, Regulatory Project Manager, at 301-827-6422. If the issue cannot be resolved at the division level, you may formally request reconsideration according to our guidance for industry titled *Formal Dispute Resolution: Appeals Above the Division Level* (February 2000). The guidance can be found at http://www.fda.gov/cder/guidance/2740fnl.htm.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation ODE II
Center for Drug Evaluation and Research

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/s/

Mary Parks
8/6/02 04:14:06 PM
for Dr. Orloff

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	Thursday April 6, 2000
TIME:	2:00 pm
LOCATION:	3rd floor Parklawn, Conference Room "M"
APPLICATION:	NDA 20-866 – Cycloset (bromocryptine)
MEETING CHAIR:	David Orloff, M.D., Deputy Director, Division of Metabolic and Endocrine Drug Products (DMEDP), HFD-510
MEETING RECORDER:	Jena Weber, Project Manager

FDA ATTENDEES, TITLES, Division of Metabolic and Endocrine Drug Products (DMEDP), HFD-510 and others:

Solomon Sobel, M.D.	Deputy Director	ORU, HFD-020
John Jenkins, M.D.	Office Director, ODE II	HFD-102
Stephen Fredd, M.D.	Deputy Division Director	HFD-110
Judy Staffa, Ph.D.	OPDRA	HFD-440
Evelyn Rodriquez, M.D.	OPDRA	HFD-440
Robert Misbin, M.D	Clinical Reviewer	DMEDP, HFD-510
Bruce Schneider, M.D.	Clinical Reviewer	DMEDP, HFD-510
Saul Malozowski, M.D.	Team Leader, Clinical	DMEDP, HFD-510
William Koch, R.Ph.	Project Manager	DMEDP, HFD-510
Jena Weber, BS	Project Manager	DMEDP, HFD-510
Lee-Ping Pian, Ph.D.	Biometrics Reviewer	HFD-715
Todd Sahlroot, Ph.D.	Biometrics Team Leader	HFD-715
Kathleen Uhl, M.D.	OND	HFD-970

ErgoScience Corporation ATTENDEES AND TITLES:

David Burt	President, ErgoScience
Marcia Testa, M.D.,Ph.D.	Harvard School of Public Policy
Anthony Cincotta, Ph.D.	Director, ErgoScience
David Adams	Counsel to ErgoScience

Proposed Indication: For the treatment of patients with Type 2 Diabetes Mellitus.

Purpose of meeting: Strategies for proceeding with the development of Cycloset for NDA approval.

Background: NDA 20-866 was initially submitted on August 18, 1997. A **not approvable** letter citing deficiencies of efficacy and safety (particularly possible adverse cardiac effects) was issued on November 20, 1998. The company provided a complete response to this letter on April 15, 1999. An **approvable** letter was issued by the Agency on October 15, 1999. Deficiencies in the clinical, biopharmaceutics, and pharmacology and toxicology sections of the application were cited.

General Discussion Points:

As specified in our approvable letter, a large, simple trial design to address clinical deficiencies was suggested. A safety study enrolling approximately 3000 subjects (diagnosed with type 2 DM) may suffice. Sample size should be justified based on study efficacy and safety objectives. The Agency will require a minimum of 2000 subjects on drug, and 1000 on placebo, treated for 6 months to 1 year. Near complete follow-up will be critical with ascertainment of vital and critical status, including as myocardial infarction (MI's), stroke and death.

An independent safety data monitoring board should be established. In addition, ADA guidelines regarding goals of therapy and standards of patient care should be followed. Patients may be enrolled who are currently taking anti-diabetic medications, but NOT thiazolidinediones (TZD's).

The protocol(s) for this/these studies should be submitted to the Agency for our review and comment before the trial(s) commence(s).

If the sponsor pursues a lipid-lowering indication, results of and adequate and well-controlled studies must be presented.

Conclusions: The sponsor will submit a detailed, study protocol(s) for Agency review and comment.

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/s/

David Orloff
8/1/02 02:56:58 PM

Endocrinologic and Metabolic Drugs Advisory Committee #70

Food and Drug Administration
Center for Drug Evaluation and Research

Holiday Inn Bethesda, 8120 Wisconsin Avenue, Bethesda, MD

May 14, 1998

Agenda

NDA 20-866, Ergoset™ (bromocryptine) Ergo Science

8:00 Call to Order, Introductions, Opening Comments
Robert Sherwin, M.D., Acting Chair
Endocrinologic and Metabolic Drugs Advisory Committee
Meeting Statement: Kathleen Reedy, Executive Secretary
Endocrinologic and Metabolic Drugs Advisory Committee

8:15 Open Public Hearing

8:45 Ergo Science Presentation

10:15 Break

10:30 FDA Presentation
Medical Review: G. Alexander Fleming, M.D., Group Leader,
Division of Metabolic and Endocrine Drug Products

Statistical Review: Lee Ping Pian, Ph.D.,
Office of Epidemiology and Biostatistics
Division of Biometrics II

11:30 Lunch

1:00 Discussion and Questions

Break

5:00 Adjourn

Endocrinologic and Metabolic Drugs Advisory Committee #70

Food and Drug Administration
Center for Drug Evaluation and Research

Holiday Inn Bethesda, 8120 Wisconsin Avenue, Bethesda, MD

May 14, 1998

NDA 20-866, Ergoset™ (bromocryptine mesylate) Ergo Science

Questions

1. Are the study designs adequate to assess the efficacy and safety of this drug for the proposed patient population?

2. What is the clinical significance of the reduced HbA1c levels observed in the pivotal studies?

3. What is the appropriate role of the prospectively stated responder analysis in the evaluation and/or labeling of this therapy?

4. Based on the efficacy and safety data presented, and your assessment of the overall benefits compared to the risks of bromocryptine therapy, do you recommend that this drug be approved for use in the proposed patient population?

5. If approval is recommended, what measures should be taken after approval to refine understanding of this therapy's efficacy and resolve its remaining safety issues.