CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-732

Administrative/Correspondence

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: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-732

NAME OF APPLICANT / NDA HOLDER
Valera Pharmaceuticals, Inc.

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)
Vantas

ACTIVE INGREDIENT(S)	STRENGTH(S)
histrelin acetate	50 mg

DOSAGE FORM
subdermal implant

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 file 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
6,361,797	3/26/2002	1/26/2020

d. Name of Patent Owner	Address *(of Patent Owner)*	
Hydro Med Sciences now Valera Pharmaceuticals, Inc.	8 Clarke Drive	
	City/State Cranbury, NJ	
	ZIP Code 08512-3617	FAX Number *(if available)* 609-409-1650
	Telephone Number 609-409-9010	E-Mail Address *(if available)* wgray@valerapharma.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)	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

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)

	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

rug 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 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, 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 *(as listed in the patent)*	Does the patent claim 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 approved labeling.)*	

5. No Relevant Patents

	For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to ch a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in anufacture, 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
William B Gray	12/02/2003

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 Valera Pharmaceuticals, Inc.	
Address 8 Clarke Drive	City/State Cranbury, New Jersey
ZIP Code 08512-3617	Telephone Number (609) 409-9010
FAX Number *(if available)* (609) 409-1650	E-Mail Address *(if available)* wgray@valerapharma.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

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

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

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
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NAME OF APPLICANT / NDA HOLDER
Valera Pharmaceuticals, Inc.

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TRADE NAME (OR PROPOSED TRADE NAME)
Vantas

ACTIVE INGREDIENT(S)	STRENGTH(S)
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DOSAGE FORM
subdermal implant

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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
5,292,515	3/8/1994	3/8/2011

d. Name of Patent Owner	Address *(of Patent Owner)*	
Hydro Med Sciences now Valera Pharmaceuticals, Inc.	8 Clarke Drive	
	City/State Cranbury, NJ	
	ZIP Code 08512-3617	FAX Number *(if available)* 609-409-1650
	Telephone Number 609-409-9010	E-Mail Address *(if available)* wgray@valerapharma.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)	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

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)

	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

Drug Product (Composition/Formulation)

	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 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, 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 *(as listed in the patent)* — Does the patent claim 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 approved labeling.)*	

5. No Relevant Patents

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

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
William B Gray	12/2/2003

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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 Valera Pharmaceuticals, Inc.	
Address 8 Clarke Drive	City/State Cranbury, New Jersey
ZIP Code 08512-3617	Telephone Number (609) 409-9010
FAX Number *(if available)* (609) 409-1650	E-Mail Address *(if available)* wgray@valerapharma.com

The public reporting burden for this collection of information has been estimated to average 9 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.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

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

General Information

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- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
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First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

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2. Drug Substance (Active Ingredient)

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2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

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

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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
5,266,325	11/30/1993	11/30/2010

d. Name of Patent Owner
Hydro Med Sciences now
Valera Pharmaceuticals, Inc.

Address *(of Patent Owner)*
8 Clarke Drive

City/State
Cranbury, NJ

ZIP Code	FAX Number *(if available)*
08512-3617	609-409-1650
Telephone Number	**E-Mail Address *(if available)***
609-409-9010	wgray@valerapharma.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)

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

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)

	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

Drug Product (Composition/Formulation)

	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 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, 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 *(as listed in the patent)*	Does the patent claim 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 approved labeling.)*	

5. No Relevant Patents

	For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in 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
William B Gray	12/2/2003

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 Valera Pharmaceuticals, Inc.	
Address 8 Clarke Drive	City/State Cranbury, New Jersey
ZIP Code 08512-3617	Telephone Number (609) 409-9010
FAX Number *(if available)* (609) 409-1650	E-Mail Address *(if available)* wgray@valerapharma.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

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

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY

NDA #	**21-732**
Trade Name Requested	**Vantas™**
Generic Name	**histrelin implant**
Applicant Name	**Valera Pharmaceuticals,**
HFD-	**580**
Approval Date	**October, 12, 2004**

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES/_X__/ NO /__/

   b) Is it an effectiveness supplement? YES /__ / NO /_X__/

   If yes, what type (SE1, SE2, etc.)?

   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 /_X__/ 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 /_X__/

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 /_X__/

* The indicated disease/condition (palliative treatment of advanced prostate cancer) does not exist in children.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /_X_/ NO /___/

If yes, NDA#: 19-836
Drug Name: Supprelin (histrelin acetate) injection

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 # _____ _____

NDA # _____ _____

2. Combination product. N/A

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 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 9:**

(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:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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 /___/

Investigation #3 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:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(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 /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(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"):

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #_3, Study # _____

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 # __ YES /_ _/ ! NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain:

Investigation #3

IND # _____ YES /_ __/ ! NO /___/ Explain:

Investigation #4

IND # _____ YES /_ __/ ! NO /___/ Explain:

Investigation #5

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 /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ 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: _____

_____

_____

{See appended electronic signature page}

Nenita Crisostomo, R.N.
Signature of Preparer

October 12, 2004
Date

Title: Project Manager

*{See appended electronic signature page}*Date: October 12, 2004

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products; HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 21-732
HFD-580/Division File
HFD-580/RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21732 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: December 12, 2004 Action Date: October 12, 2004

HFD-580 Trade and generic names/dosage form: Vantas (histrelin acetate) Implant

Applicant: Valera Pharmaceuticals, Inc. Therapeutic Class: 3S

Indication(s) previously approved: Supprelin (histrelin acetate) was originally approved under NDA 19-836 in 1991 for treatment of central precocious puberty. The postmarketing commitment to complete a "Phase 4 long-term follow-up study of patients with central precocious puberty who were treated with supprelin" was fulfilled in November 17, 1998 and therefore released from the commitment. The NDA was withdrawn by then sponsor Shire Laboratories in December 2002.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication: Palliative Treatment of Advanced Prostate Cancer

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

X Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____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
X Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
X Other: The indicated disease state, prostate cancer, is listed in the FDA guidance as a disease that has no applicability to pediatric patients and only occurs in adults.

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:

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

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
☐ 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:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

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**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

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:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Nenita I. Crisostomo, R.N.
Regulatory Project Manager

cc: NDA
HFD-960/ Grace Carmouze
(revised 12-22-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

Attachment A

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

Indication #2: _____

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

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

☐ **No: Please check all that apply: ____Partial Waiver ____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:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

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**
☐ **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:

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

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**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

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

ction D: Completed Studies

Age/weight range of completed studies:

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

Comments:

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.

This page was completed by:

{See appended electronic signature page}

Nenita I Crisostomo, R.N.
Regulatory Project Manager

cc: NDA
HFD-960/ Grace Carmouze
(revised 10-14-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

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

/s/

Nenita Crisostomo
10/12/04 12:44:38 PM

VALERA
Pharmaceuticals

RECEIVED
MAR 0 3 2004
FDR/CDER

February 23, 2004

To: Document Control Room
Division of Reproductive and Urologic Drug Products (HFD-580)
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

From: William B. Gray
Senior Director of Regulatory Affairs

Enclosed please find duplicate copies of original letter sent on February 20, 2004.

Appears This Way
On Original

8 Clarke Dr., Cranbury, NJ 08512-3617 p 609-409-9010 f 609-409-1650 www.valerapharma.com

Via Certified Mail and Facsimile Transmission

VALERA Pharmaceuticals

February 20, 2004

DANIEL SHAMES, M.D., DIRECTOR
Division of Reproductive and Urologic Drug Products (HFD-580)
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Telephone: 301.827.4260
Facsimile: 301.827.4267

Product Name: **Histrelin Subdermal Implant**
NDA No: **21-732**
Re: **REQUEST FOR WAIVER OF PEDIATRIC STUDIES**

Dear Dr. Shames,

Reference is made to our submission of NDA No. 21-732 histrelin acetate (implant) for the palliative treatment of advanced prostate cancer.

In accord with the *Draft Guidance for Industry Recommendations for Complying with the Pediatric Rule* (21 CFR § 314.55(a), Valera Pharmaceuticals Inc. requests a full waiver of all pediatric studies as a disease-specific waiver. The Vantas™ (histrelin acetate) implant is indicated for the treatment of palliative treatment of advanced prostate cancer in adults.

Our reason for requesting the waiver is the indicated disease state, prostate cancer, is listed in the FDA guidance as a disease that has extremely limited applicability to pediatric patients in that the signs and symptoms of this disease occur for the most part in the adult population.

Should you require additional information or have any questions, please contact me directly at 609.409.9010, extension 224 or via email at wgray@valerapharma.com .

Kind Regards,

William B. Gray
Senior Director Regulatory Affairs

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. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
21-732

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Valera Pharmaceuticals Inc.	2/20/04
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
609 409 9010	609 409 1650
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
8 Clarke Drive Cranbury, NJ 08512	

PRODUCT DESCRIPTION

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

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY	
histrelin subdermal implant	Vantas	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*		**CODE NAME** *(If any)*
histrelin acetate		
DOSAGE FORM:	**STRENGTHS:**	**ROUTE OF ADMINISTRATION:**
subdermal implant	50 mg	implant

(PROPOSED) INDICATION(S) FOR USE:
alliative treatment of advance prostate cancer

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
Pediatic waiver request

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.

8 Clarke Drive
Cranbury, NJ 08512

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

NDA 19-836 Supprelin Injection- Roberts Pharmaceuticals Corporation

	's 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 (FDA 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)* Pediatric waiver request

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:
[signature]	William Gray, Sr. Director Regulatory Affairs	2/20/04

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
6 Clarke Drive, Cranbury, NJ 08512	(609) 409 9010

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:

nent of Health and Human Services
nd Drug Administration
, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

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.

VALERA
Pharmaceuticals

DEBARMENT CERTIFICATION STATEMENT

Valera Pharmaceuticals Inc. 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

William Gray
Senior Director
Valera Pharmaceuticals Inc.

8 Clarke Dr., Cranbury, NJ 08512-3617 p 609-409-9010 f 609-409-1650 www.valerapharma.com

10-12-04

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA **21-732**	Efficacy Supplement Type SE-	Supplement Number	
Drug: **Vantas™ (histrelin implant)**		Applicant: **Valera Pharmaceuticals, Inc.**	
RPM: **Nenita Crisostomo, R.N.**		HFD-**580**	Phone # **301-827-7260**
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): **NDA 19-836, Supprelin (histrelin acetate) injection**	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	October 12, 2004
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
Exclusivity Summary (approvals only)	October 12, 2004

Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	September 17, 2004
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	none generated after October 8,2004
• Most recent applicant-proposed labeling	October 8, 2004
• Original applicant-proposed labeling	December 12, 2003
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	
◦ DDMAC ◦ DMETS—Trade Name Review ◦ DSRCS—Patient Information	July 6, 2004 March 6, 2004 June 8, 2004
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	none generated after 10/8/04 submission
• Applicant proposed	October 8, 2004
• Reviews	
◦ Chemistry Review #1	June 15, 2004
◦ Chemistry Review #2	September 23, 2004
◦ Chemistry Review #3	October 8, 2004
◦ DMETS	March 6, 2004
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	September 24, 2004
• Documentation of discussions and/or agreements relating to post-marketing commitments	Sponsor submissions dated September 30 and October 1, 2004
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	12/24/03, 2/24/04, 3/22/04, 5/24/04, 6/10/04, 6/17/04, 6/22/04, 7/14/04, 7/26/04, 8/2/04, 8/9/04, 8/17/04, 8/23/04, 9/1/04, 9/27/04
❖ Memoranda and Telecons	August 5, 2004
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	December 19, 2001
• Pre-NDA meeting (indicate date)	August 12, 2003
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A

Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	
• Division Director	See Medical Team Leader's Memo
• Medical Team Leader	October 12, 2004
❖ Clinical review(s) *(indicate date for each review)*	October 8, 2004
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See Clinical Review, Oct. 8, 2004
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	February 25, 2004
❖ Statistical review(s) *(indicate date for each review)*	N/A
❖ Biopharmaceutical review(s) *(indicate date for each review)*	October 7, 2004
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	#1-June 15, 2004 #2-September 23, 2004 #3-(Memo) October 8, 2004
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	CMC Review #2, page 18, 9/23/04
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	CMC Review #2, page 18, 9/23/04
Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	Review#1: July 14, 2004 Review #2: Sept. 14, 2004 Review #3: (memo) Sept. 21, 2004
❖ Facilities inspection (provide EER report)	Date completed: October 4, 2004 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (X) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	September 13, 2004
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	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/

Nenita Crisostomo
10/12/04 01:17:33 PM

DUPLICATE

VALERA Pharmaceuticals

Via Fedex

N 000 BL
ORIG AMENDMENT

October 8, 2004

DANIEL SHAMES, M.D., DIRECTOR
Division of Reproductive and Urologic Drug Products (HFD-580)
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Telephone: 301.827.4260
Facsimile: 301.827.4267

RECEIVED
OCT 0 8 2004
FDR/CDER

Product Name: **Histrelin Implant**
NDA No: **21-732**
Re: **DRAFT LABELING PACKAGING 10-8-2004**

Dear Dr. Shames,

Reference is made to our submission dated December 12, 2003 of NDA No. 21-732 histrelin acetate (implant) for the palliative treatment of advanced prostate cancer.

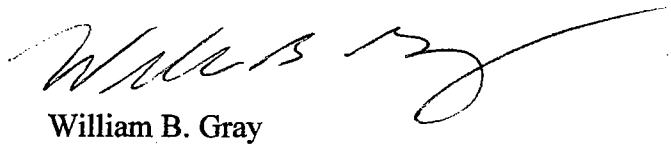
Attached for your review are the following revised draft labeling as discussed yesterday:

1. Secondary carton
2. Implant carton label
3. Pouch and vial label
4. Implant kit carton label
5. Implantation devise pouch label
6. Overshipper carton

The attached labeling has been revised to add the agreed to presentation of the trade name VANTAS.

Should you require additional information or have any questions, please contact me directly at 609.409.9010, extension 224 or via email at wgray@valerapharma.com .

Kind Regards,



William B. Gray
Senior Director Regulatory Affairs
Valera Pharmaceuticals Inc.

33 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

VALERA
Pharmaceuticals

Via Fedex

October 1, 2004
DANIEL SHAMES, M.D., DIRECTOR
Division of Reproductive and Urologic Drug Products (HFD-580)
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Telephone: 301.827.4260
Facsimile: 301.827.4267

Product Name: **Histrelin Implant**
NDA No: **21-732**
Re: **RESPONSE TO FDA TELECONFERENCE ON SEPTEMBER 24, 2004**
Phase IV Study Commitment Amendment

Dear Dr. Shames,

Reference is made to our submission dated December 12, 2003 of NDA No. 21-732 histrelin acetate (implant) for the palliative treatment of advanced prostate cancer.

Further reference is made to the teleconference between Valera and the Division dated September 24, 2004. During this teleconference the Division requested Valera provide a commitment to a Phase IV study which was sent on September 30, 2004.

At this time, Valera would like to clarify the proposed date for completion of the study and generated report will be October 31, 2006.

Should you require additional information or have any questions, please contact me directly at 609.409.9010, extension 224 or via email at wgray@valerapharma.com .

Kind Regards,

William B. Gray
Senior Director Regulatory Affairs
Valera Pharmaceuticals Inc.

VALERA
Pharmaceuticals

Via FedEx

September 30, 2004

DANIEL SHAMES, M.D., DIRECTOR
Division of Reproductive and Urologic Drug Products (HFD-580)
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Telephone: 301.827.4260
Facsimile: 301.827.4267

Product Name: **Histrelin Implant**
NDA No: **21-732**
Re: **RESPONSE TO FDA TELECONFERENCE ON SEPTEMBER 24, 2004**
Phase IV Study Commitment

Dear Dr. Shames,

Reference is made to our submission dated December 12, 2003 of NDA No. 21-732 histrelin acetate (implant) for the palliative treatment of advanced prostate cancer.

Further reference is made to the teleconference between Valera and the Division dated September 24, 2004. During the teleconference the Division requested that Valera provide a commitment to a Phase IV study, accordingly:

Valera commits to perform a post-approval study investigating 10 patients with difficult to locate or nonpalpable implants. The study will collect information on these patients utilizing the instructions in the physician label, including specialized investigations such as ultrasound and CT scan, to aid in the location and removal of the implant. The data from the study will be provided as a report to the Agency.

Proposed study timelines:

December 15, 2004: Study protocol written and sent to the FDA

January 31, 2005: Upon acceptance by the FDA and IRB approval study starts

(We anticipate patients who may qualify for the study to be formally included by 2006, this will be the one year mark (12 month implant) when the patients are due for

re-implantation)

The study status will be included in the IND No. 40,772 Annual Report.

When 10 patients have been attained in the study, a report will be generated and provided to the Agency within two months.

Should you require additional information or have any questions, please contact me directly at 609.409.9010, extension 224 or via email at wgray@valerapharma.com .

Kind Regards,

William B. Gray

William B. Gray
Senior Director Regulatory Affairs
Valera Pharmaceuticals Inc.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-732

9/27/04

Valera Pharmaceuticals, Inc.
Attention: William B. Gray, M.S.
Senior Director, Regulatory Affairs
8 Clarke Drive
Cranbury, NJ 08512-3617

Dear Mr. Gray:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for histrelin implant.

We are currently reviewing your application and have the following comments.

The development of the proposed IVIVC has limitations in that only mean data from the pivotal trial lots was employed in demonstrating the *in vitro-in vivo* correlation rather than individual lot data. More importantly, the correlation was not validated using either internal or external data for the determination of predictability error. The submitted data therefore, cannot be considered a validated and acceptable IVIVC.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Health Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
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/

Daniel A. Shames
9/27/04 06:27:02 PM

9/17/04

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA# **21-732**
Trade Name: Vantas™
Generic Name: histrelin acetate subdermal implant
Strengths: 50 mcg per day, continuous release for one year
Applicant: Valera Pharmaceuticals, Inc.

Date of Application: December 12, 2003
Date of Receipt: December 12, 2003
Date of Filing Meeting: January 20, 2004
Filing Date: February 10, 2004

Indication(s) requested: Palliative Treatment of Advanced Prostate Cancer

Type of Application: Original (b)(1) NDA **X** Original (b)(2) NDA _____
(b)(1) Supplement _____ (b)(2) Supplement _____
[If the Original NDA was a (b)(2), all supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or a (b)(2).]

If the application is a 505(b)(2) application, complete the 505(b)(2) section at the end of this summary.

Therapeutic Classification: S **X** P _____
Resubmission after a withdrawal _____ or refuse to file _____
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) _____

Has orphan drug exclusivity been granted to another drug for the same indication? YES **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)]?
NA YES NO

Is the application affected by the application integrity policy (AIP)? YES **NO**
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? **NA** YES NO

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

Form 3397 (User Fee Cover Sheet) submitted: YES NO
User Fee ID # **4682**
Clinical data? YES **X** NO _____, Referenced to NDA # **19-836**
Date clock started after UN: _____

User Fee Goal Date: **October 12, 2004**

Action Goal Date (optional): _____

- Does the submission contain an accurate comprehensive index? **YES** NO

- Was form 356h included with an authorized signature? **YES** NO
  If foreign applicant, both the applicant and the U.S. agent must sign.

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

- If an electronic NDA, does it follow the Guidance? **N/A** YES NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format? **NONE**

  Additional comments: **The sponsor initially tried to submit the NDA electronically, but in a wrong format and later resorted to paper NDA**

- If in Common Technical Document format, does it follow the guidance? **N/A** YES NO

- Is it an electronic CTD? N/A YES **NO**
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- Patent information included with authorized signature? **YES** NO

- Exclusivity requested? YES, _____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** NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. 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 the studies listed in Appendix ____." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure information included with authorized signature? **YES** NO
  (Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)

- Has the applicant submitted pediatric waiver request for all ages and indications?
  NEED TO REVISE OR DELETE THIS STATEMENT
  YES NO
- If no, explain.

- Field Copy Certification (that it is a true copy of the CMC technical section)? **YES** NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? **YES** NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? **NO**
  If not, have the Document Room make the corrections. **Corrected on March 9, 2004**

- List referenced IND numbers: **IND 40772**

- End-of-Phase 2 Meeting? Date **December 19, 2001** NO
  If yes, distribute minutes before filing meeting.
  **No official meeting, but this meeting will serve as End-of Phase 2 meeting because it served as a guidance to the final revisions of the Phase 3 program.*

- Pre-NDA Meeting(s)? Date(s) **August 12, 2003** NO
  If yes, distribute minutes before filing meeting.

Project Management

- Package insert consulted to DDMAC? **YES** NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? **YES** NO

- MedGuide and/**or PPI** (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support?
  N/A **YES** NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of Surveillance, Research and Communication Support?
  N/A YES NO

- Has DOTCDP been notified of the OTC switch application? **N/A** YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  N/A YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? **YES** NO
  If no, did applicant submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? **YES** NO
- If parenteral product, consulted to Microbiology Team (HFD-805)? **YES** NO

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #:
- 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").
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

  YES NO
- Is 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 should be refused for filing under 314.101(d)(9).

  YES NO
- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 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.

  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

  ____ 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. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

____ 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.)
____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:
  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES NO
  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    YES NO
  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    N/A YES NO
  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    N/A YES NO
- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):
  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    YES NO
  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES NO
  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

    YES, IND # _____ NO

    OR
    A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

    N/A YES NO
- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

  YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 20, 2004

BACKGROUND:
The drug product, Vantas™ subdermal implant (histrelin acetate) is a sterile implantable hydrogel cartridge (3 cm X 3.5mm) containing 50mg of histrelin acetate. It is designed to deliver histrelin acetate at a controlled rate of 50mcg per day for a 12-month therapeutic period. At the end of a year, it must be removed and replaced with another Vantas™ implant.

ATTENDEES:

Mark Hirsch, M.D. - Medical Team Leader, DRUDP (HFD-580)
Ashok Batra, M.D. - Medical Officer, DRUDP (HFD-580)
Harry Handelsman, D.O. - Medical Officer, DRUDP, HFD-580
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP, HFD-580
Suong Tran, Ph.D. - Chemist, DNDC II @ DRUDP (HFD-580)
DJ Chatterjee, Ph.D. – Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Martin Kauffman, DOD, Regulatory Project Manager, DRUDP (HFD-580)
Nenita Crisostomo, R.N. - Regulatory Project Manager, DRUDP, HFD-580

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Ashok Batra, M.D.-Filing Harry Handelsman, D.O.-Action
Secondary Medical:	Mark Hirsch, M.D.
Statistical:	Mike Welch, Ph.D.
Pharmacology:	Krishan Raheja, D.V.M., Ph.D
Statistical Pharmacology:	N/A
Chemist:	Suong Tran, Ph.D.
Environmental Assessment (if needed):	DMPQ
Biopharmaceutical:	Dhruba Chatterjee, Ph.D.-Filing Sandhya Apparaju, Ph.D.-Action
Microbiology, sterility:	James McVey, M.S.
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	
Center for Devices and Radiological Health	Viola Hibbard, R.N.
Project Manager:	Nenita Crisostomo, R.N.

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

CLINICAL FILE **X** REFUSE TO FILE _____

- Clinical site inspection needed: YES **NO**

- Advisory Committee Meeting needed? YES, date if known _____ **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	YES	NO
CLINICAL MICROBIOLOGY	FILE ___	REFUSE TO FILE ____		**N/A**
STATISTICAL	FILE **X**	REFUSE TO FILE ____		
BIOPHARMACEUTICS	FILE **X**	REFUSE TO FILE ____		
• Biopharm. inspection needed:			YES	**NO**
PHARMACOLOGY	FILE **X**	REFUSE TO FILE ____		
• GLP inspection needed:			YES	**NO**
CHEMISTRY	FILE **X**	REFUSE TO FILE ____		
• Establishment(s) ready for inspection?			**YES**	NO
• Microbiology			**YES**	NO

ELECTRONIC SUBMISSION: **NO**
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

X The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ The application is unsuitable for filing. Explain why:

ACTION ITEMS:

1. The Project Manager will forward the following documents to the appropriate divisions for consultative reviews:

   a. Physician Insert and container/carton labeling (immediate vial labeling, vial carton package labeling, vial carton, secondary implant carton labeling, secondary implant carton, kit primary carton labeling, kit primary carton, trocar labeling, corrugate overshipper, corrugate overshipper label) to the Division of Medication Errors and Technical Support (DMETS) for evaluation of tradename, Vantas™

   b. Patient Summary Information and Insertion/Removal Procedures to the Division of

Surveillance, Research, and Communication Support (DSRCS)

c. Physician Insert to the Division of Drug Marketing, Advertising and Communication (DDMAC)

2. Items to be included in the 74-day filing issues letter: All reviewers will forward review issues to Project Manager who will process the letter conveying these issues. See Filing letter to sponsor.

Prepared by:

{see appended electronic signature}

Nenita Crisostomo, R.N.
Regulatory Project Manager, HFD-580

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LRipper/1-10-03

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/s/

Nenita Crisostomo
9/17/04 11:39:57 AM
CSO

Nenita Crisostomo
9/17/04 11:41:56 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-732

9/9/04

Valera Pharmaceuticals, Inc.
Attention: William B. Gray, M.S.
Senior Director, Regulatory Affairs
8 Clarke Drive
Cranbury, NJ 08512-3617

Dear Mr. Gray:

Please refer to your December 12, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for histrelin acetate implant.

We also refer to the meeting between representatives of your firm and the FDA on August 5, 2004. The purpose of the meeting was to discuss the current unresolved review issues.

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 Nenita Crisostomo, R.N., Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Mark Hirsch, M.D.
Clinical Team Leader
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE

DATE/TIME: August 5, 2004, 11:30 A.M. – 12:30 P.M.

APPLICATION #: NDA 21-732, histrelin acetate subdermal implant

BETWEEN:

Name: David Tierney, M.D. – President and CEO Valera Pharmaceuticals
Petr Kŭzma, Vice President, M.S. – Research & Development
Matt Rue, Vice President – Marketing
Martin Dineen, M.D. – Principal Clinical Investigator
[redacted] – Clinical Consultant
David Clissold – Regulatory Consultant, Hyman, Phelps & McNamara, P.C.
Heather M. Irish – Ass. Director, Clinical Data Management

Phone: 1-800-563-3954

Representing: Valera Pharmaceuticals, Inc.

AND

Name: Mark S. Hirsch, M.D. – Clinical Team Leader
Harry Handelsman, D.O. – Clinical Reviewer
Sandhya Apparaju, Ph.D. – Pharmacokinetics Reviewer
Nenita Crisostomo, R.N. – Regulatory Project Manager

Representing: Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Review Issues

BACKGROUND: Valera Pharmaceuticals, Inc. submitted this new drug application (NDA) dated December 12, 2003. The User Fee Goal date is October 12, 2004. Currently on its 8th month into the review cycle, the Division arranged for this teleconference to apprise the sponsor of the current unresolved review issues as listed below:

1. Vantas as a trade name is not recommended.
2. Review of trochar#3 experience to date.
3. Implant "losses."
4. Difficult retrievals of implants.

The Sponsor submitted three flowcharts immediately prior to the teleconference.

DISCUSSIONS:

1. **Trade Name**—The Division informed the Sponsor that due to the look-alike/sound-alike issues, Vantas is not recommended by the Division of Medication Errors and Technical Support (DMETS). The Division discussed these issues with Sponsor and provided choices for their subsequent action regarding the trade name. The Sponsor will submit alternative trade names to the Division for new review by DMETS. An advice letter containing DMETS comments will be sent to the Sponsor.

2. **Trochar #3 experience to date**—The Sponsor reports that out of the 104 patients re-implanted since April 2003, 65 patients were implanted using trochar #3. Of these, 56 patients are actively participating at 52 weeks of treatment. Forty-one (41) of them were re-implanted with trochar #3, 14 patients were discontinued, and 10 patients with pending re-implantation as of July 12, 2004. Of the 39 patients who were re-implanted with an alternative method since April 2003, 13 of them were re-implanted with trochar #3. Further details, including any available data of those newly re-implanted that were not included in the July Safety Update, will be included in the August submission. Per Sponsor, data collection cut-off date is August 12, 2004 and this final safety update will be submitted around the week of August 18, 2004.

   The Division inquired about the reasons for the discontinuation in 14 patients who had been implanted using trochar #3, prior to the end of 52 weeks. Sponsor stated that discontinuation of treatment did not have anything to do with the implant, nor were there any expulsion-related problems. Reasons for the discontinuation include: disease progression, hospice situations, closing of study site, etc. The Sponsor will submit a summary of this information.

   The Division requested that the Sponsor submits line listings of these patients to include specific reasons for discontinuation for each patient.

   The Division also requested sponsor to submit the new implantation instructions instituted in April 2003. This is part of the review documents and will serve as evidence in support of the NDA and will be useful for labeling.

3. **Unable to locate implant**—The Division inquired about the specific details and management of the following eight patients in whom the implant could not be located:

   a. # 301-06-004
   b. # 301-07-002
   c. # 301-03-005
   d. # 301-22-002
   e. # 302-05-001
   f. # 302-19-001
   g. # 301-06-009
   h. # 301-22-002

   The Sponsor will provide a narrative account for each of these patients, including the reason for the inability to locate their implants. The sponsor will also include the specific clinical intervention that was implemented for each patient listed.

   The Division recommended that information in the Patient Information and Physician Insert should include information in regard to this issue, including, but not limited to: patient responsibilities in self-monitoring (self-palpation) and clinic visits (frequency, testosterone levels) to ensure presence of implant, and, guidance for physicians who cannot find or palpate the implant.

   Sponsor stated that the "algorithm" for clinical management of a missing implant was included in the 120-day Safety Update submitted in June and they will re-submit. The

Sponsor agreed to highlight in the labels the standard of medical practice of clinic visits every 6 months in addition to checking the efficacy of the drug and the presence/placement of the implant.

The Sponsor will submit a summary of these recommendations, based on the aforementioned eight patients, to change the labels.

4. **Difficult to remove the implant**—The Division stated that patients and physicians should be aware that difficulty in implant removal is a potential problem related to tissue reactions, fibrosis, etc. Step-by-step instructions of the insertion procedures should be clearly stated in the Physician Insert—this should include who is qualified to perform the procedure. The patient and prescriber should be informed of the possible difficulty in removing the implant. Include in the Product Information all possible techniques to minimize this problem. Physicians and patients should not be surprised in the physician's office during the procedure.

   The Sponsor further added other reasons for such difficulties: the implant is placed too deeply, and the tip of the knife to incise the pseudo-capsule can sever the implant into two pieces. The sponsor agreed to include appropriate verbiage in the labels to address this problem. Revisions to the labels will be submitted in 1-2 weeks.

SUMMARY:

1) Project Manager will draft the Advice letter regarding DMETS review of the trade name.
2) Sponsor will submit alternative proprietary drug names.
3) Sponsor will include, in the final Safety Update, an account of total experience with trochar #3 to date, line listings for the discontinued patients prior to 52 weeks, and a summary of reasons for the discontinuations.
4) The Sponsor will submit a copy of the new instructions for the implantation procedure instituted in April 2003.
5) The sponsor will submit a comprehensive accounting of those patients whose implants could not be located.
6) The sponsor will submit an "algorithm" for management of patients in whom implants could not be located.
7) The Sponsor will submit the revised labels in 1-2 weeks.

Concurred By:

{see appended electronic signature}

Mark S. Hirsch, M.D.
Clinical Team Leader

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/s/

Mark S. Hirsch
9/9/04 02:53:30 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: August 23, 2004

To: William Gray Senior Director, Regulatory Affairs	**From:** Nita Crisostomo, RN Project Manager
Company: Valera Pharmaceuticals	Division of Division of Reproductive and Urologic Drug Products
Fax number: 609-409-1650	**Fax number:** 301-827-4267
Phone number: 609-409-9010 x 224	**Phone number:** 301-827-4260

Subject: NDA 21-732 histrelin acetate subdermal implant—CMC Informational Request, in reference to your 8/9/04 submission

Total no. of pages including cover: 2

Comments:

Hello Bill,

Here is the CMC Information Request I spoke to you about on the phone today. It has been circulated, however, we can only transmit via facsimile at this time due to network problems. We shall wait for your response as soon as possible.

Thank you very much,

Nita

Document to be mailed: ☑ YES ☐ NO

Attachment/nic

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

9-1-04

NDA 21-732

INFORMATION REQUEST LETTER

Valera Pharmaceuticals, Inc.
Attention: William B. Gray, M.S.
Senior Director, Regulatory Affairs
8 Clarke Drive
Cranbury, NJ 08512-3617

Dear Mr. Gray:

Please refer to your December 12, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for histrelin acetate subdermal implant.

We also refer to your submission dated August 9, 2004.

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

1. Provide qualification information to justify the proposed [ ] limit for [ ] in the drug substance specification.
2. Revise the post-approval stability commitment to add the underlined in the following statement: "The first three commercial batches and an annual batch thereafter will be subjected to stability testing as defined in Valera Post-Approval Stability Protocol."

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Health Project Manager, at 301-827-4260.

Sincerely,

{see appended electronic signature}

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products, HFD-580
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
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NDA 21-732
Vantas™ (histrelin implant)
Valera Pharmaceuticals

PUBLIC COMMUNICATION

No public communication was required for this application.

6 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

NDA 21-732
Vantas™ (histrelin implant)
Valera Pharmaceuticals

CLINICAL INSPECTION

Clinical Inspections are not required for this application by the decision of the Division of Reproductive and Urologic Drug Products Clinical Team and the Division of Scientific Investigations. No indication for clinical inspections.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

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

Date: August 19, 2004

From: Viola Hibbard, Nurse Consultant
DAGID/GHDB, HFZ-480

Through: Anthony Watson, Branch Chief, CDRH/ODE/DAGID/GHDB, (HFZ-480)

Subject: Addendum for Consult Review for NDA 21-732

To: Suong Tran, Ph.D.
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products

CC: Nenita Crisostomo, R.N., RPM

This consult is an addendum to the previous consult dated June 29, 2004.

In a response dated July 22, 2004, the sponsor wrote the following: "Pyrogen Test Method: Not Applicable. This statement indicates that with the different sterilization method, they would not be doing the pyrogen testing. This point needed clarification because on April 13, 2004, the sponsor had provided adequate information in response to this question. At that time, they stated that [redacted] testing was done and the result was that the testing performed on the finished device had passed the USP endotoxin limits.

In the April 13, 2004 information, the sponsor stated that for the commercial production, the company would switch from [redacted] sterilization to [redacted] The device review question at this point was would any of the sterilization criteria change with a different sterilization method. The sponsor provided the SAL, validation method and [redacted] but stated as noted above that the pyrogen test was not applicable. The question is do they plan to not do the pyrogen testing with the [redacted] method of sterilization to be used for the commercial production of the device. This testing should be done no matter which sterilization method is used.

A telephone conference call was made on August 18, 2004 to get clarification on the pyrogen testing for both sterilization methods. Dr. Suong Tran, Chemist and Nenita Crisostomo, RPM from CDER, Viola Hibbard, Reviewer/CDRH were the FDA participants. William Gray, Senior Director Regulatory Affairs and Les Heiman, Valera Associate Director of QA were the sponsor participants in the conference call.

In the telephone conference, the sponsor representatives clarified that the pyrogen testing will be done as indicated in the April information for [ ] sterilization method as well as [ ] method that has been done before. Nenita requested that the sponsor provide this information in writing to CDER to include in the file. Based on their explanation, they thought that since they chose not to put the pyrogen free claim on the labeling that they would not have to address this point any further. I explained to them that they may chose to leave off the labeling the statement "pyrogen free" but we need to know that the testing was done and the method used to do the test.

The information from Valera Pharmaceuticals was forwarded from CDER to CDRH (August 23, 2004) to answer the request for the additional information and clarification of the July 22, 2004 correspondence. The sponsor has adequately addressed the question.

Viola Hibbard

Viola Hibbard
VSH@CDRH.fda.gov
301-594-1287 X173

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

REQUEST FOR CONSULTATION

'Division/Office):
:ctor, Division of Medication Errors and Technical Support,
D-420, Parklawn, Room 6-34
Attention: Sammie Beam
Denise Toyer, Pharm.D.

FROM: Nenita Crisostomo, Project Manager
Division of Reproductive and Urologic Drug Products
Phone: 301-827-7260

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
August 18, 2004		21-732	New NDA—2nd Trade Name Proposal	August 6, 2004

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Vantas (histrelin acetate implant)	ASAP	GnRH agonist	September 9,, 2004

NAME OF FIRM: Valera Pharmaceuticals, Inc.

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
- X PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER **Proposal of new Trade Name**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW END OF PHASE II MEETING ONTROLLED 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:

Ms. Beam & Ms. Toyer,

The sponsor submitted 3 alternative trade names after being informed that "Vantas" was not recommended due to the sound-alike/look-alike issues. Please re-evaluate. Attached is a hard copy of their submission dated August 6, 2004, indicating the 3 alternative trade names: 1 [illegible]

3 The User Fee Goal Date is October 12, 2004. Please call me if you have any questions.

Thank you,
Nita Crisostomo

Cc: Mark Hirsch, Harry Handelsman, Su Tran, Carol Holquist

NATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL X HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Nenita Crisostomo
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-732

8-17-04

Valera Pharmaceuticals, Inc.
Attention: William B. Gray, M.S.
Senior Director, Regulatory Affairs
8 Clarke Drive
Cranbury, NJ 08512-3617

Dear Mr. Gray:

Please refer to your December 12, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for histrelin acetate subdermal implant.

The Division of Medication Errors and Technical Support (DMETS) has reviewed the labels and labeling from a safety perspective and has the following comments and information requests. DMETS has identified several areas of possible improvement, which might minimize potential user error. We request a prompt written response in order to continue our evaluation of your NDA.

A. CONTAINER LABEL (IMMEDIATE VIAL)

1. Increase the prominence of the established name to be at least 50% of the font size of the proprietary name.
2. Include the route of administration.
3. Reduce the prominence of the manufactured and distributed by statement.

B. AMBER POLY VIAL POUCH

See comments for the IMMEDIATE VIAL.

C. CORRUGATE OVERSHIPPER

Include the lot number and expiration date.

D. INSERT LABELING

1. DESCRIPTION Section:

   Delete the trailing zeroes presented throughout the labeling because they could be misinterpreted (e.g. 2.0 as 20).

2. CLINICAL PHARMACOLOGY SECTION Section, Absorption Subsection:

Delete the abbreviation "µg" and replace with "mcg" because "µg" is often confused with "mg." This abbreviation (µg) appears on the Institute for Safe Medication Practices' list of dangerous abbreviations.

3. PRECAUTIONS SECTION

   a. INFORMATION FOR PATIENTS Subsection

      The most important information included in the patient information leaflet should also be included in this section.

   b. GENERAL Subsection

      Include a statement regarding the fact that histrelin acetate subdermal implant is not radio-opaque and will not be visible through X-ray. In the instance where the implant is difficult to locate by palpation, ultrasound may be used.

4. Include a HOW SUPPLIED section.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Health Project Manager, at 301-827-4260.

Sincerely,

{see appended electronic signature}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products, HFD-580
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
8/17/04 09:00:51 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-732

8/9/04

Valera Pharmaceuticals, Inc.
Attention: William B. Gray, M.S.
Senior Director, Regulatory Affairs
8 Clarke Drive
Cranbury, NJ 08512-3617

Dear Mr. Gray:

Please refer to your December 12, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for histrelin acetate subdermal implant.

The Division of Medication Errors and Technical Support (DMETS) has reviewed proposed proprietary name from a safety perspective and has the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

We do not recommend the use of the proprietary name Vantas. In reviewing the proprietary name, the primary concerns related to look-alike and/or sound-alike confusion with Lantus and Zantac.

A. Vantas can sound and look similar to Lantus when pronounced or scripted. Lantus is a long-acting insulin product indicated for the treatment of diabetes. Vantas and Lantus both contain six letters. The endings of each name are almost identical ('antas' vs. 'antus') which is the greatest contribution to the look-alike and sound-alike characteristics of each name. Additionally, the first letter in each name can look similar depending on how the V or L is scripted. Furthermore, the first syllables of each name rhyme ('Van' vs. 'Lan'). The two drugs also share some similar product characteristics such as storage conditions (refrigerated) and route of administration (subcutaneous). They also share overlapping numerals in their usual doses (50 mg vs. 50 units). Although the two medications do not share dosage forms (implant vs. injection), both products are only available in one dosage form. Thus, this information can be left off of a prescription and the incorrect product could still be dispensed (i.e. Vantas 50 mg, use SC as directed vs. Lantus 50 units, use SC as directed). With the close look-alike and sound-alike characteristics of the names as well as the similarities in product characteristics, there is an increased potential for medication errors due to name confusion between Vantas and Lantus.

VANTAS
LANTUS

B. Vantas can look similar to Zantac when scripted. Zantac is a histamine antagonist indicated for duodenal and gastric ulcers, pathological hypersecretory conditions,

gastroesophageal reflux disease, erosive esophagitis, and heartburn. Vantas and Zantac both contain six letters. The middle section of both names is identical ('anta'), which is the principal contribution to the look-alike characteristics between the names. Additionally, the first letter in each name ('V' vs. 'Z') can look similar depending on how they are written. The two medications have similar product characteristics such as how supplied (50 mg implant vs. 50 mg intravenous bag and 50 mg vial) and usual dose (50 mg). Although the two products do not overlap in dosage form (implant vs. injection and capsule) or dosing interval (once every 12 months vs. every 6 to 8 hours), this distinction does not necessarily help to prevent confusion. Because the intravenous preparation of Zantac is only available in 50 mg doses, the dosage form and/or frequency could be left off a prescription and the incorrect product could still be dispensed, (i.e. Vantas 50 mg x 1 vs. Zantac 50 mg x1). Additionally, either one of these products could be ordered to the patient's bedside in order to be readily available for use by a physician. For example, many times Zantac is used to prepare patients for surgery and it may be ordered to be at patient's bedside in order to be administered before a patient is taken to the operating room. On the other hand, a physician could order Vantas to be at patient's bedside so that it may be implanted by the physician. In essence, inpatient prescriptions could be written for either Vantas or Zantac that look very similar due to the look-alike characteristics of the names along with the similar conditions of use. Overall, the look-alike similarities as well as the similarities between the product characteristics cause an increased potential for medication errors due to name confusion between Vantas and Zantac.

V A N T A S
Z A N T A C

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Health Project Manager, at 301-827-4260.

Sincerely,

{see appended electronic signature}

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader for the
Division of Reproductive and Urologic Drug Products, HFD-580
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
8/9/04 05:36:04 PM

COPY

VALERA Pharmaceuticals

Via Federal Express

August 6, 2004

DANIEL SHAMES, M.D., DIRECTOR
Division of Reproductive and Urologic Drug Products (HFD-580)
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Telephone: 301.827.4260
Facsimile: 301.827.4267

Product Name: **Histrelin Subdermal Implant**
NDA No: **21-732**
Re: **FDA teleconference 8/5/2004**

Dear Dr. Shames,

Reference is made to our submission dated December 12, 2003 of NDA No. 21-732 histrelin acetate (implant) for the palliative treatment of advanced prostate cancer.

Further reference is made to our teleconference with the Division on August 5, 2004. The Division shared a DMET consult with Valera which stated that Vantas as proprietary name is not recommended due to sound-alike/look-alike issues. Valera has decided not to pursue Vantas as a trade name for our histrelin subdermal implant.

Accordingly, we formally provide the Agency with three alternative trade names listed in order of preference below.

1 – [redacted]
2 –
3 –]

As discussed in our teleconference we ask the alternative trade names be given prompt consideration by the DMET.

Should you require additional information or have any questions, please contact me directly at 609.409.9010, extension 224 or via email at wgray@valerapharma.com .

Kind Regards,

William B. Gray
Senior Director Regulatory Affairs
Valera Pharmaceuticals Inc.
8 Clarke Drive
Cranbury New Jersey, 08512

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

8-2-04

NDA 21-732

INFORMATION REQUEST LETTER

Valera Pharmaceuticals, Inc.
Attention: William B. Gray, M.S.
Senior Director, Regulatory Affairs
8 Clarke Drive
Cranbury, NJ 08512-3617

Dear Mr. Gray:

Please refer to your December 12, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vantas™ (histrelin acetate) subdermal implant.

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

Based on the release and stability data, please revise the acceptance criteria for Elution Rate in the drug product specification to be as follows:

[ ]

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{see appended electronic signature}

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products, HFD-580
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
8/2/04 02:02:59 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

7-26-04

NDA 21-732

INFORMATION REQUEST LETTER

Valera Pharmaceuticals, Inc.
Attention: William B. Gray, M.S.
Senior Director, Regulatory Affairs
8 Clarke Drive
Cranbury, NJ 08512-3617

Dear Mr. Gray:

Please refer to your December 12, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vantas™ (histrelin acetate) subdermal implant.

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

1. Provide a complete data summary for the [ ] process validation including the [ ] process derived from this study.
2. [ ] should be added to the sterilization process specifications.
3. Identify the sterilizer(s) that will be used for the implants and their relationship to the [ ] (used for validation).
4. Provide the written procedures for reprocessing along with data summaries to support it or indicate that reprocessing is not requested at this time and will be addressed in a supplemental application when appropriate.
5. The description of biological indicators provided in the third paragraphs on page 093 in volume 12 indicates that the simulated product cartridges received from HydroMed Sciences and vialed at [ ] What organism was inoculated at [ ] and where in the simulated product was it inoculated?
6. The [ ] is noted in the validation experiment. This would not be acceptable for regular production. Significant growth could and probably would occur during this period. Provide your expected production holding periods and supporting data summaries if the holding periods are intended to exceed 72 hour refrigerated.

7. Provide a description of the record keeping system used to verify individual lot sterilization and the maintenances of those records of sterilization in the batch production records. How is this key data incorporated into the lot release system.
8. Provide in-process bioburden testing methods and acceptance levels. Include sampling points and times.
9. Refer to USP <1207> for general information on container closure integrity testing. Any of the integrity testing systems available [ ] are acceptable for initial container closure evaluation. Subsequent evaluation using the same method in the stability program is preferable.
10. The histrelin insert's endotoxin limit can be calculated as a drug product assuming total release in one hour; as if the implant were severed during insertion. You should cut the implant to address this potential problem (worst case). Provide the SOP for the method and data summaries of the inhibition/enhancement studies performed to validate the method you will use for testing this product. Include data summaries for three manufactured lots or a commitment to complete this aspect of the validation prior to marketing.
11. Indicate where and by whom the USP sterility test is performed on each lot of product released for marketing. Appropriate CFR references for this requirement are 21 CFR 211.167(a) and 21 CFR 314.50(d)(1)(ii)(a). Provide The Standard Operating Procedures (SOPs) and validation data summaries for the procedures used. The implant should be cut in order to simulate the worst case as was done in the validation study reported by [ ]

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{see appended electronic signature}

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products, HFD-580
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
7/26/04 04:59:09 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

7-14-04

NDA 21-732

INFORMATION REQUEST LETTER

Valera Pharmaceuticals, Inc.
Attention: William B. Gray, M.S.
Senior Director, Regulatory Affairs
8 Clarke Drive
Cranbury, NJ 08512-3617

Dear Mr. Gray:

Please refer to your December 12, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vantas (histrelin acetate) subdermal implant.

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

For the [ ] of the to-be-marketed implantation device (trocar), provide the [ ] dose, sterilization assurance level, validation method, pyrogen test method, and packaging of the device.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{see appended electronic signature}

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products, HFD-580
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
7/14/04 11:24:07 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

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

Date: June 29, 2004

From: Viola Hibbard, Nurse Consultant
DAGID/GHDB, HFZ-480

Through: Anthony Watson, Branch Chief, CDRH/ODE/DAGID/GHDB, (HFZ-480)

Subject: Consult Review for NDA 21-732

To: Suong Tran, Ph.D.
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products

CC: Nita Crisostomo, R.N., RPM

I. Introduction

This consult is provided as requested for CDER for a review of a device used for implantation of Vantas (histrelin implant). It is a drug/device combination designed to provide a sustained release of a steady amount of histrelin over a period of one year when implanted subdermally with the trocar device. Vantas™ is indicated in the palliative treatment of advanced prostate cancer.

II. Device Description

The insertion device was developed over time through a number of manual modifications of a tuberculin syringe. The second manual design was used in the clinical trials. A new device was designed for commercialization of this drug/device combination. Valera produced a new trocar/cannula to enhance and improve the previous implanter.

The new trocar/cannula device was designed by [ ] and manufactured by [ ] for Valera. This insertion tool is composed of [ ]. The cannula is controlled by a button, which is extended to hold the implant. The implant is inserted in the open end of the cannula. The implanter is inserted under the skin up to the depth line on the cannula. To insert the implant, the thumb pulls the implanter button back; then, the implanter is removed from the insertion site, leaving the Histrelin implant under the skin. The device handle geometry is designed to assure a proper shallow approach, controlled by guiding the cannula subcutaneously and not intramuscularly. The geometry is supposed to assure a handgrip that effectively maintains the back-up piston stationary as the cannula retracts relative to the capsule. This new device was then used by Valera for use in the clinical trial of 65 patients.

The shell, scoop and post of the device are made of [ ] The cannula is made of stainless steel and has a tip protector made of [ ]

III. Consult Review Issues

Consult review questions submitted to CDER on February 9, 2004 for the filing letter.

CDRH Review Issues

A. You have provided the history of how the device has evolved and manufacturing processes. Please provide a description of the **finished** device used in the clinical trial. In the description, please include the following: the type of plastic along with a brief narrative description used for each of the multi-pieces used to make the insertion trocar, and the type of stainless steel used to make the cannula.

The firm has adequately addressed this in the information dated April 13, 2004 that was submitted in response to the filing letter of February 24, 2004 (see Section II above).

B. On page 004 and other sections, the use of a button on the device is used to remove the implanter and leave the Histrelin implant under the skin. Please provide a brief summary of testing done (bench and clinical) to assure that this feature functions as intended.

The firm tests the Trocars assembled to verify function and general appearance. 100% of the Trocars are also tested to verify the button/cannula slides freely and functions as intended.

Valera [ ] specifies that each lot of the implantation device is to be sampled based on [ ] The samples are tested for functionality.

Clinical testing was done using the device on 66 patients. Table 3 indicates that of the devices used, four had functionality problems. One comment stated that the "Trocar not great," one implant lodged in the Trocar and the Implant broke, there was difficulty in loading the implant and the Trocar tended to shear plastic coating off implant, and with Patient # 35, the first implant would not release from trocar because the implant appeared to have "sheared on edge". That one was replaced with a second implant and placed without difficulty. Please see Section IV B below.

C. In Section 4.4.6 you have provided sterilization information including the method [ ] and the dosages that were established to attain the sterility. Please provide the Sterility Assurance Level (SAL) and the type of packing used to maintain the sterility of the device. Was — testing done on the final finished device? If so, did that testing show that it has passed the testing?

The SAL should have been determined. The testing and substantiation of [ ] done according to [ ] is acceptable. LAL testing was done on the finished device and was less than [ ] The samples passed the USP endotoxin limit as defined in USP 25-NF 20, January 2002. The Trocar was packaged in [ ]

The company has stated that for commercial production, they will employ [ ] [ ] which will be conducted by [ ] Sterilization information that should be provided for the commercial production are listed in Section IV C.

D. Please provide test results for biocompatibility according to [ ] for the device component that has blood and tissue contact.

The needle is [ ] stainless steel and is the only component that contacts blood or tissue. The company has provided biocompatibility testing results according to [ ] Endotoxin testing was done and revealed no evidence of material-mediated pyrogenicity.

E. Device and all package labeling for the final finished product (device) should be provided for review.

For a finished device, CDRH/ODE labeling includes the name of the device; needles should include the length and gauge, single use only, a notation regarding sterility and package integrity, and the prescription legend. This is in addition to the instructions for use. Since this is a kit, you may have this information included on the box or other labels as appropriate.

IV. Conclusion and Recommendations

A. Information that the sponsor has submitted related to Manufacturing and Control Sections has not been evaluated in this consultative review. Only the sections that describe the container closure system as a finished device were considered. We believe that the manufacturing information is a Quality Systems issue with GMP implications that should be addressed by CDER as the lead review center. Perhaps the Office of Combination Products should help decide which GMPs will be involved in this NDA review process.

B. The clinical use of the Trocar with 66 patients indicates that there was a problem with the functionality of four of the Trocars. The question that needs to be addressed with the appropriate reviewers in CDER and the CDRH consultant is the following: Does the problems identified with three of the Trocars warrant any further questions about design and functionality? The fourth problem seemed to be rather vague and insignificant based on the information provided. Is this the general number of problems that may be associated with implant devices? The other question that we may consider is the potential problem of user error or technique. Is there a need for a labeling revision and user education? This may be a review issue.

C. The sterilization assurance level was not formally determined by Valera using the [ ] method. Determination of the SAL should be done for any sterile device for this intended use. The SAL should be

For the commercial production, [ ] will be done. Please provide the [ ] validation method, pyrogen test method and packaging of the device if any of these points are different from the current sterilization method.

Thank you.

Viola Hibbard

Viola Hibbard, RN., BSN
VSH@CDRH.fda.gov
301-594-1287 X173

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-732

INFORMATION REQUEST LETTER

Valera Pharmaceuticals, Inc.
Attention: William B. Gray, M.S.
Senior Director of Regulatory Affairs
8 Clarke Drive
Cranbury, NJ 08512-3617

6-22-04

Dear Mr. Gray:

Please refer to your December 12, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vantas™ (histrelin acetate) subdermal implant.

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

1. Be advised that the Drug Master File (DMF [redacted] for histrelin acetate is currently deficient. A deficiency letter was sent by FDA to the DMF holder on May 6, 2004, delineating the issues of concern.
2. Provide the drug substance specification in the NDA, and it should be revised as discussed in the DMF deficiency letter.
3. On page 042 of Volume 3, explain why the acceptance criteria for Purity and Assay of the active ingredient are different from those in the drug substance specification in the DMF.
4. Revise the acceptance criteria for Related Impurities and Residual Solvents as discussed in the DMF deficiency letter.
5. Provide a complete composition table of the drug product to include:
   - the target weights of histrelin acetate and stearic acid in one finished implant (sterilized and primed).
   - the target total weight of one finished implant.
   - the target volume of — sodium chloride used to store one finished implant (i.e., per vial).
6. Provide the specifications for the( )
7. Confirm that the component — Saline Solution Sterile, USP" used in the storage solution of the implant is in fact — Sodium Chloride Irrigation, USP.
8. Provide test results or certificates of analysis for all components used to manufacture Lots 508, 510, and 511.

9. Provide data to show that no [ ] can be detected on the polymer cartridge [ ]

10. Clarify the quality of the – Sodium Chloride Solution used to hydrate the implants (is it the same – Sodium Chloride Irrigation, USP, used to manufacture the storage solution?)

11. Indicate the number of polymer cartridges that are sent to Quality Control for testing (this information is not included in the master batch record).

12. Clarify whether the reprocessing is the repeating of specific manufacturing steps that are part of the described process or it includes steps that are different from the described process.

13. Clarify when the expiration dating period of the finished implant (sterilized and primed) begins.

14. Provide a clarification on the acceptance criteria for [ ] proposed in the specification for the polymer cartridge. – Of concern is the following possibility: [ ]

15. [ ] results are provided on pages 173-174 of Volume 6 for the [ ] cartridges, [ ] used for Lot 511. Clarify the designations [ ] on page 174 (are the polymer cartridges [ ] In addition, provide an explanation for the absence of this test in the in-process material specification for the [ ]

16. In order to assess the in-process material controls for the hydrated implants, provide information on the development of the hydration process. Such information should include a report on the structural characterization of the hydrogel and a summary of how the different factors in the hydration process were optimized [ ]. A rationale for the 1.8% Sodium Chloride storage solution and its volume of 2 mL should also be provided. In addition, justify the absence of tests [ ] hydrogel [ ] Discuss the correlation (or lack of) between these parameters and the drug release property of the hydrogel matrix.

17. Provide an explanation for [ ] (results on page 032 of Volume 344) in light of the statement on page 043 of Volume 344 that [ ]

18. For all three clinical lots 508, 510, and 511, provide complete batch analysis results for all analytical procedures included in the proposed drug product specification.

19. Provide a justification for the absence of [ ] in the drug product specification.

20. Revise the acceptance criteria for [ ] to state a target amount and range (i.e., "approximately" is not adequate).

21. Regarding the HPLC analytical procedure [ ] "Assay for the Determination of Histrelin and Related Substances in the Histrelin Subdermal Implant, Post Sterilization":
    a. Because [ ] is poorly resolved from histrelin, add the following requirement to the system suitability testing: [ ]
    b. Provide sample calculations for Histrelin Base in Implant and Vial, % Label Claim Histrelin, and % Impurities/Degradation products in the Implant (equations page 015 of Volume 4) as well as the associated chromatograms.
    c. Provide a post-approval agreement to develop, fully validate, and implement a revised HPLC analytical procedure that will have a better resolution for [ ] (refer to USP guidelines on chromatography.) This agreement should be fulfilled within a year of the NDA approval.
22. Provide sample calculations for elution rates on Day 1 and at Weeks 3 and 4 (equations on page 027 of Volume 4) as well as the associated chromatograms.
23. Provide the manufacturers' certificates of analysis for the glass vials and stoppers used in Lots 508, 510, and 511.
24. Regarding the stability of the drug product, provide the following:
    a. Sterility data at the end of the proposed shelf life.
    b. A stability commitment and post-approval stability protocol as follows:
        1) The stability commitment should include:
            i. The first three commercial batches will be placed on stability. Subsequently, a minimum of one lot per year will be placed on stability.
            ii. The results of the ongoing studies will be submitted in the annual reports.
            iii. Any extension of the expiry will be based on full real-time data for three production lots generated according to the stability protocol.
            iv. The applicant will withdraw any lot that fails specifications during the expected shelf life unless the deviation is discussed with the FDA reviewing division and receives approval for continuing distribution.
        2) The post-approval stability protocol should include a specification and a testing schedule. The stability specification should include [ ] Testing Schedule should follow ICH guidelines.
25. The claim for a categorical exclusion from an environment assessment cites 21 CFR 25.24 (page 001 of Volume 5), which does not exist. Provide a correct reference for the claim.
26. Regarding the Method Validation package, provide a list of samples to be submitted to FDA labs, with the batch/lot numbers and sample amounts, as well as batch analysis results for

these samples. Samples to be submitted should include both the drug product and the drug substance.

27. The established name must be consistent throughout all labeling (package inserts and packaging labels). The established name should be "histrelin subdermal implant" because "histrelin" is designated USAN. Therefore, the name of the product should be

    Vantas (histrelin subdermal implant) 50 mg*
    *Each implant contains 50 mg of histrelin acetate to deliver 41 mg of histrelin.

28. There should be a label on an outside carton stating the complete contents of the Vantas system (i.e., composed of both implant and implantation kit). Such a label should state the following:

    Top of carton:

    Front of carton:

Right and left sides of carton:

Back side of carton:

A package insert, patient information, and insertion and removal instructions

29. The secondary carton label should be revised as follows (add the underlined to the proposed text):

2 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

33. The implantation device pouch label should be revised as follows (add the underlined to the proposed text, delete the crossed out):

[ ]

Sterile for Single Use Only.

[ ]

Rx only

34. Provide mock-up labels complete with graphics and colors.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{see appended electronic signature}

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader for the
Division of Reproductive and Urologic Drug Products, HFD-580
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
6/22/04 10:10:41 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

6-17-04

NDA 21-732

INFORMATION REQUEST LETTER

Valera Pharmaceuticals, Inc.
Attention: William B. Gray, M.S.
Senior Director, Regulatory Affairs
8 Clarke Drive
Cranbury, NJ 08512-3617

Dear Mr. Gray:

Please refer to your December 12, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vantas (histrelin acetate) subdermal implant.

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

Provide the following data in an electronic format:

For **all** the patients in the pivotal study # 301 (Phase 3 study), provide the individual patient histrelin concentration versus time data in SAS format, along with the patient demographics, disease state and renal/hepatic function status. Include the available histrelin data from all pharmacokinetics (PK) patients, as well as non-PK patients of this study.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
6/17/04 12:19:54 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

6/10/04

NDA 21-732

INFORMATION REQUEST LETTER

Valera Pharmaceuticals, Inc.
Attention: William B. Gray, M.S.
Senior Director, Regulatory Affairs
8 Clarke Drive
Cranbury, NJ 08512-3617

Dear Mr. Gray:

Please refer to your December 12, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vantas (histrelin acetate) subdermal implant.

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

Provide an executive summary of the three cases (Patient #001, 004, and 005 from Study #301, Site #9), with apparent testosterone surges at the time of the indicated second implant. Include individual narratives for each patient in this response.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
6/10/04 01:24:53 PM

MEMORANDUM

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

DATE: June 8, 2004

TO: Dan Shames, M.D. Director
Division of Reproductive and Urologic Drug Products
HFD-580

VIA: Nita Crisostomo, Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products
HFD-580

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for Vantas (histrelin acetate implant), NDA 21-732

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for Vantas (histrelin acetate implant), NDA 21-732. It has been reviewed by our Office and by DDMAC. We have simplified the wording, made it consistent with the PI, removed promotional language and other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications, not to provide detailed information about the condition), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. These revisions are based on draft labeling submitted December 12, 2003.

We also have the following comment:

We recommend expanding the PRECAUTIONS section, *Information for Patients* subsection of the PI to include important counseling information for the Physician to provide to the patient. The sponsor has not stated how the patient is to receive this PPI. Patients usually only receive PPIs when the are packaged in unit-of-use packaging and dispensed directly to the patient. This device is only used in physician offices; it is not dispensed directly to the patient.

Comments to the review Division are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division. Please call us if you have any questions.

Patient Information
Vantas™ *(DSRCS Comment: Add the phonetic spelling.]*
(histrelin acetate implant)

Read the Patient Information that comes with VANTAS before it is inserted and each time another Vantas™ is inserted. There may be new information. This information does not take the place of talking with your doctor about your medical condition or treatment.

What is Vantas™?
Vantas™ is a drug-delivery system that contains the medicine histrelin and is placed under the skin. It looks like a small, thin flexible tube. After it is placed under the skin, Vantas™ delivers histrelin to your body continuously for 12 months. Vantas may help relieve the symptoms of prostate cancer. Vantas is not a cure for prostate cancer.

Who should not use Vantas™?
Do not use Vantas if you:
- **are allergic to the medicine histrelin** or other medicines called GnRH agonists.
- **are a woman.** Vantas™ has not been studied in women and is not for any use in women. Vantas™ may harm the unborn baby in a woman who is pregnant or may become pregnant. Vantas may cause a pregnant woman to lose her baby (miscarriage) if used while pregnant.
- **are a child under 18 years.** Vantas™ has not been studied in children and should not be used in children.

Before using Vantas, tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. It is not known if Vantas and other medicines can affect each other.

How is Vantas™ used?
- Vantas is placed under the skin of the inside of your upper arm. Your doctor will numb your arm, make a small cut (incision), and then place Vantas™ under the skin.

What are the possible side effects of Vantas™?
Vantas can cause an increase in testosterone during the first week after it is inserted. Your symptoms may get worse for a few weeks. You may get new symptoms. Call your doctor right away if you:

- get new or worse bone pain
- get weakness or lose feeling in your legs
- have blood in your urine
- have trouble urinating or cannot urinate

Vantas can cause a loss in bone mineral density. Low bone mineral density can lead to thinning of the bones (osteoporosis).

The most common side effects of Vantas™ are:

- hot flashes
- tiredness
- skin reactions at the implant insertion site
- testicles become smaller
- [illegible]
- breasts become larger
- erectile dysfunction (impotence)
- constipation

You may have some pain at the insertion site during and after Vantas™ is inserted and removed. You may get some bruising and redness at the site. These usually go away without treatment within 2 weeks. Call your doctor if you have unusual bleeding, redness or pain at the insertion site.

These are not all the side effects of Vantas. For more information, ask your doctor or pharmacist.

General information about Vantas
This leaflet summarizes the most important information about Vantas. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Vantas that is written for health professionals. You can also visit www.valerapharma.com on the Internet.

Rx Only
Manufactured by
Valera Pharmaceuticals, Inc.
Cranbury, NJ 08512 U.S.A.

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

/s/

Jeanine Best
6/8/04 02:21:35 PM
DRUG SAFETY OFFICE REVIEWER

Gerald DalPan
6/8/04 02:32:19 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

5/24/04

NDA 21-732

INFORMATION REQUEST LETTER

Valera Pharmaceuticals, Inc.
Attention: William B. Gray, M.S.
Senior Director, Regulatory Affairs
8 Clarke Drive
Cranbury, NJ 08512-3617

Dear Mr. Gray:

Please refer to your December 12, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vantas™ (histrelin acetate) subdermal implant.

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

For the Phase II Study # BAR-002-0591A-USA, provide data for the individual histrelin concentration versus time.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Acting Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
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/

Jennifer L. Mercier
5/24/04 11:59:23 AM

VALERA Pharmaceuticals

Via Facsimile and Via Federal Express

April 30, 2004

Dr. Sue Tran, Chemistry Reviewer
Division of Reproductive and Urologic Drug Products (HFD-580)
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Telephone: 301.827.4260
Facsimile: 301.827.4267

Product Name: **Histrelin Subdermal Implant**
NDA No: **21-732**
Re: **Amendment**
Chemistry information request

Dear Dr. Tran,

Reference is made to our submission dated December 12, 2003 of NDA No. 21-732 histrelin acetate (implant) for the palliative treatment of advanced prostate cancer.

Further reference is made to your telephone request for additional information regarding the cleaned packaging vials.

Accordingly, provided herewith is the requested information:

Vials are [redacted] For your reference I have include the Summary [redacted] Process used by the vendor to clean the vials.

This process includes; [redacted]

certificate of analysis. Valera intends to have this level verified by an outside laboratory, [redacted]

Vendor addresses:

Glass vials:

[ ]

Vials are cleaned and certified in the Certificate of Analysis (CoA) which is provided by;

[ ]

The CoA ( ) will be initially verified by a **contract lab;**

[ ]

Should you require additional information or have any questions, please contact me directly at 609.409.9010, extension 224 or via email at wgray@valerapharma.com .

Kind Regards,

William B. Gray
Senior Director Regulatory Affairs
Valera Pharmaceuticals Inc.
8 Clarke Drive
Cranbury, NJ 08512
Phone: 609-409-9010 ext 224
Fax: 609-409-1650

Enclosure: [ ]

CC: Nenita Crisostomo

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. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
21-732

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Valera Pharmaceuticals Inc.	4/30/04
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
609 409 9010 ext 224	609 409 1650
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
8 Clarke Drive Cranbury, NJ 08512	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(if previously issued)*

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY	
histrelin subdermal implant	Vantas	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*		**CODE NAME** *(if any)*
histrelin acetate		
DOSAGE FORM:	**STRENGTHS:**	**ROUTE OF ADMINISTRATION:**
dermal implant	50 mg	implant

PROPOSED) INDICATION(S) FOR USE:
For palliative treatment of advance prostate cancer

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
Chemistry reviewer request for information on vial packaging

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.

8 Clarke Drive
Cranbury, NJ 08512

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

NDA 19-836 Supprelin Injection- Roberts Pharmaceuticals Corporation

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)* Chemistry reviewer request for information on vial packaging

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:
Walter B Gray	William Gray, Sr. Director Regulatory Affairs	4/30/04

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
8 Clarke Drive, Cranbury, NJ 08512	(609) 409 9010

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
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

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.

1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

3/22/04

NDA 21-732

INFORMATION REQUEST LETTER

Valera Pharmaceuticals, Inc.
Attention: William B. Gray, M.S.
Senior Director, Regulatory Affairs
8 Clarke Drive
Cranbury, NJ 08512-3617

Dear Mr. Gray:

Please refer to your December 12, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vantas™ (histrelin acetate) implant.

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

In response to the Division's pre-NDA meeting (Aug 12, 2003) comment that "consideration should be given to the specificity limitations of the radioimmunoassay (RIA), to address ADME," you provided the following information:

- A brief mention regarding an LC/MS/MS method currently under development for assay of histrelin in plasma; you expressed an intention to analyze the duplicate samples from the Phase I pharmacokinetic (PK) study, for validation of the LC/MS/MS technique.
- An investigation of antiserum cross-reactivity, employing eleven potential cross-reactants (ten different histrelin fragments and LHRH). The results of this study demonstrate high cross-reactivity with at least 4 different peptide fragments.

To support your submission, provide, if available, the results obtained from the analysis of the duplicate samples from the 500 µg subcutaneous (SC) bolus dose study, employing the LC/MS/MS method. In addition, explain the *in vivo* relevance of the potential cross reactants assayed employing RIA. Provide the basis for your understanding whether or not these fragments will occur in plasma. If so, provide the concentrations.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
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/

Margaret Kober
3/22/04 02:00:32 PM
Chief, Project Management Staff

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**ODS CONSULT #:** 04-0087
March 6, 2004	July 5, 2004 **PDUFA DATE:** October 12, 2004	

TO: Daniel Shames, MD
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Nenita Crisostomo
Project Manager
HFD-580

PRODUCT NAME:	**NDA SPONSOR:** Valera Pharmaceuticals, Inc.
Vantas™ (Histrelin Acetate Implant) 50 mg **NDA#:** 21-732	

SAFETY EVALUATOR: Kristina C. Arnwine, PharmD

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, Vantas.

   DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name Vantas acceptable from a promotional perspective.

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 30, 2004

NDA#: 21-732

NAME OF DRUG: Vantas™ (Histrelin Acetate Implant)

NDA HOLDER: Valera Pharmaceuticals, Inc.

NOTE: This review contains proprietary and confidential information that should not be released to the public.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580), for assessment of the proprietary name, Vantas, regarding potential name confusion with other proprietary or established drug names. Container labels, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Vantas, is a sterile nonbiodegradable, diffusion controlled miniature implantable drug delivery device designed to deliver histrelin for 12 months at a controlled rate. Histrelin, an LH-RH agonist, is a potent inhibitor of gonadotropin secretion when given continuously. After implantation Vantas delivers 50-60 mcg per day over 12 months. Vantas must be removed after 12 months of therapy. Vantas is supplied in an amber poly vial pouch inside of a carton containing one implant.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Vantas to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise

[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.
[4] WWW location http://www.uspto.gov/tmdb/index.html.

was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Vantas. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Vantas acceptable from a promotional perspective.

2. The Expert Panel identified four proprietary names that were thought to have the potential for confusion with Vantas. These products are listed in table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Vantas	Histrelin Acetate Implant 50 mg	One implant per year	
Lantus	Insulin Glargine Injection 100 units/mL	2 units to 100 units SC once daily	SA/LA
Vantin	Cefpodoxime Proxetil Tablets, 100 mg and 200 mg Granules for Suspension, 50 mg/5 mL & 100 mg/mL	100 mg to 400 mg by mouth twice daily	SA/LA
Zantac	Ranitidine Tablets, 75 mg, 150mg, 300 mg 150 mg effervescent tablets Syrup 15 mg/mL Injection 50 mg/50 mL bag and 50 mg 2 mL vial	50 mg IV every 6 to 8 hours or 150 mg by mouth 1 to 4 times daily	LA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Vantas were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Vantas with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 124 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Vantas (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Vantas as dir in clinic today #1	"Please give him 1 Vantas implant to be used in clinic today. Dispense 1."
Inpatient RX: Vantas to be implanted today	

2. Results:

Two respondents interpreted the proposed name as Vantin. Vantin is a currently marketed U.S. product. See Appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

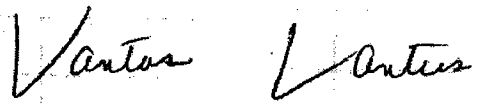
<u>NOTE</u>: This review contains proprietary and confidential information that should not be released to the public.

In reviewing the proprietary name Vantas, the primary concerns related to look-alike and sound-alike confusion with [ ] Lantus, Vantin, and Zantac. Additionally, the established name looks similar to histamine. DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Vantas could be confused with Vantin. Two respondents from the verbal study misinterpreted the name for an already existing marketed drug product. Although there are limitations to the predictive value of these studies, primarily due to sample size, we have acquired safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

1. Vantas can sound and look similar to Lantus when pronounced or scripted. Lantus is a long-acting insulin product indicated for the treatment of diabetes. Vantas and Lantus both

contain six letters. The endings of each name are almost identical ('antas' vs. 'antus') which is the greatest contribution to the look-alike and sound-alike characteristics of each name. Additionally, the first letter in each name can look similar depending on how the V or L is scripted. Furthermore, the first syllables of each name rhyme ('Van' vs. 'Lan'). The two drugs also share some similar product characteristics such as storage conditions (refrigerated), route of administration (subcutaneous) and they can also share overlapping numerals in their usual doses (50 mg vs. 50 units). Although the two medications do not share dosage forms (implant vs. injection), both products are only available in one dosage form. Thus, this information can be left off of a prescription and the incorrect product could still be dispensed (i.e. Vantas 50 mg, use SC as directed vs. Lantus 50 units, use SC as directed). With the close look-alike and sound-alike characteristics of the names as well as the similarities in product characteristics, there is an increased potential for medication errors due to name confusion between Vantas and Lantus.

V A N T A S
L A N T U S



2. Vantas can look similar to Zantac when scripted. Zantac is a histamine antagonist indicated for duodenal and gastric ulcers, pathological hypersecretory conditions, gastroesophageal reflux disease, erosive esophagitis, and heartburn. Vantas and Zantac both contain six letters. The middle of both names are identical ('anta'), which is the principal contribution to the look-alike characteristics between the names. Additionally, the first letter in each name ('V' vs. 'Z') can look similar depending on how they are written. The two medications have similar product characteristics such as how supplied (50 mg implant vs. 50 mg intravenous bag and 50 mg vial) and usual dose (50 mg). Although the two products do not overlap in dosage form (implant vs. injection and capsule) or dosing interval (once every 12 months vs. every 6 to 8 hours), this distinction does not necessarily help to prevent confusion. Since the intravenous preparation of Zantac is only available in 50 mg doses, the dosage form and/or frequency could be left off a prescription and a product could still be dispensed, (i.e. Vantas 50 mg x 1 vs. Zantac 50 mg x1). Additionally, either one of these products could be ordered to the patient's bedside in order to be readily available for use by a physician. For example, many times Zantac is used to prepare patients for surgery and it may be ordered to be at patient's bedside in order to be administered before a patient is taken to the operating room. On the other hand, a physician could order Vantas to be a patient's bedside so that it may be implanted by the physician. In essence, inpatient prescriptions could be written for either Vantas or Zantac that look very similar due to the look-alike characteristics of the names along with the similar conditions of use. Overall, the look-alike similarities as well as the similarities between the product characteristics cause an increased potential for medication errors due to name confusion between Vantas and Zantac.

V A N T A S
Z A N T A C

<u>NOTE</u>: This review contains proprietary and confidential information that should not be released to the public.

3. ⌜

⌟

4. Vantas and Vantin can sound similar when pronounced and look similar when scripted. Vantin is a cephalosporin antibiotic indicated for the treatment of infections of the upper and lower respiratory tract, skin and skin structures, urinary tract, as well as sexually transmitted diseases. Vantas and Vantin both contain six letters. The beginnings of both names are identical ('Vant'), which is the principal basis for the look-alike and sound-alike characteristics. Although the letters in the ending of the names are different, they can look similar depending on how they are scripted. Additionally, the two products share an overlapping strength (50 mg vs. 50 mg/5 mL). In contrast, there are different product characteristics such as route of administration (subcutaneous vs. oral), dosage form (implant vs. tablets and granules for suspension), dosing frequency (once every 12 months vs. twice daily), and usual dose (50 mg vs. 100 mg to 400 mg). Despite the sound-alike and look-alike characteristics along with the similarities in how the products are supplied, the product characteristics help to decrease the potential for medication errors due to name confusion between Vantas and Vantin.

VANTAS
VANTIN

5. The established name Histrelin can look similar to Histamine when scripted. Histamine is a biologically active amine found in many tissues. Histamine is used clinically to diagnose gastric hypersecretory conditions and to differentiate asthma from other pulmonary conditions. Histamine and Histrelin both begin with 'Hist' and both contain nine letters which are the greatest contributions to the look-alike similarities between the names. However, the endings of each name are different ('relin' vs. 'amine'). Additionally, histamine is not commercially available in the United States. Thus, the lack of commercial

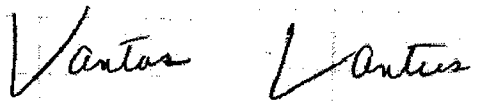
availability decreases the potential for medication errors due to name confusion between histrelin and histamine.

II. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name Vantas. In reviewing the proprietary name, the primary concerns related to look-alike and/or sound-alike confusion with Lantus, and Zantac.

A. Vantas can sound and look similar to Lantus when pronounced or scripted. Lantus is a long-acting insulin product indicated for the treatment of diabetes. Vantas and Lantus both contain six letters. The endings of each name are almost identical ('antas' vs. 'antus') which is the greatest contribution to the look-alike and sound-alike characteristics of each name. Additionally, the first letter in each name can look similar depending on how the V or L is scripted. Furthermore, the first syllables of each name rhyme ('Van' vs. 'Lan'). The two drugs also share some similar product characteristics such as storage conditions (refrigerated), route of administration (subcutaneous) and they can also share overlapping numerals in their usual doses (50 mg vs. 50 units). Although the two medications do not share dosage forms (implant vs. injection), both products are only available in one dosage form. Thus, this information can be left off of a prescription and the incorrect product could still be dispensed (i.e. Vantas 50 mg, use SC as directed vs. Lantus 50 units, use SC as directed). With the close look-alike and sound-alike characteristics of the names as well as the similarities in product characteristics, there is an increased potential for medication errors due to name confusion between Vantas and Lantus.

V A N T A S
L A N T U S



B. Vantas can look similar to Zantac when scripted. Zantac is a histamine antagonist indicated for duodenal and gastric ulcers, pathological hypersecretory conditions, gastroesophageal reflux disease, erosive esophagitis, and heartburn. Vantas and Zantac both contain six letters. The middle of both names are identical ('anta'), which is the principal contribution to the look-alike characteristics between the names. Additionally, the first letter in each name ('V' vs. 'Z') can look similar depending on how they are written. The two medications have similar product characteristics such as how supplied (50 mg implant vs. 50 mg intravenous bag and 50 mg vial) and usual dose (50 mg). Although the two products do not overlap in dosage form (implant vs. injection and capsule) or dosing interval (once every 12 months vs. every 6 to 8 hours), this distinction does not necessarily help to prevent confusion. Since the intravenous preparation of Zantac is only available in 50 mg doses, the dosage form and/or frequency could be left off a prescription and a product could still be dispensed, (i.e. Vantas 50 mg x 1 vs. Zantac 50 mg x1). Additionally, either one of these products could be ordered to the patient's bedside in order to be readily available for use by a physician. For example, many times Zantac is used to prepare patients for surgery and it may be ordered to be at patient's bedside in order to be administered before a patient is taken to the operating room. On the other hand, a physician could order Vantas to be a patient's bedside so that it may be implanted by the physician. In essence, inpatient prescriptions could be written for either Vantas or Zantac that look very similar due to the look-alike characteristics of the names along with the similar conditions of use. Overall, the look-alike similarities as well as the similarities between the product characteristics cause an increased potential for medication errors due to name confusion between Vantas and Zantac.

V A N T A S
Z A N T A C

Additionally, DMETS reviewed the labels and labeling from a safety perspective. DMETS has identified several areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL (IMMEDIATE VIAL)

1. Increase the prominence of the established name.

2. We note the strength is based on the active moiety. Thus, we suggest revising the labels and labeling in one of the three following formats.
   (Note: DMETS prefers choice 'a'.)

   1. Vantas
   (Histrelin Implant)
   41 mg

   2. Vantas
   (Histrelin Acetate Implant)
   50 mg*

   *Each implant contains histrelin acetate equivalent to 41 mg of histrelin.

   3. Vantas
   (Histrelin Acetate Implant)
   equivalent to 41 mg histrelin

3. Include the route of administration.

4. Include a net quantity statement if space permits.

5. Reduce the prominence of the manufactured and distributed by statement.

B. AMBER POLY VIAL POUCH

See comments A-1 through A-5.

C. CARTON LABELING (VIAL CARTON PACKAGE)

1. See Comments A-2 and A-3.

2. Relocate the net quantity statement to the principal display panel.

D. SECONDARY IMPLANT CARTON LABELING

1. The carton should contain a statement on the principal display panel such as, "This carton contains 1 vial containing Vantas (Histrelin Implant), 1 ice pack, etc.

2. Include storage conditions.

3. Include the lot number and expiration date.

E. KIT PRIMARY CARTON LABELING

Include the statement "To be used with Vantas (Histrelin Implant) only."

F. TROCAR LABELING (contained within the kit)

Include the statement, "To be used with the Vantas (Histrelin Implant) Implantation Kit only."

G. CORRUGATE OVERSHIPPER

1. See Comment D-1.

2. Include the lot number and expiration date.

3. Include storage instructions.

H. INSERT LABELING

1. DESCRIPTION Section:

Delete the trailing zeroes presented throughout the labeling since they could be misinterpreted (e.g. 2.0 as 20).

2. CLINICAL PHARMACOLOGY SECTION Section, Absorption Subsection:

Delete the abbreviation "µg" and replace with "mcg" since "µg" is often confused with "mg". This abbreviation (µg) appears on the ISMP's list of dangerous abbreviations.

3. PRECAUTIONS SECTION

a. INFORMATION FOR PATIENTS Subsection

All information included in the patient information leaflet should also be included in this section.

b. GENERAL Subsection

Include a statement regarding the fact that Vantas [redacted] through CT, [redacted]

4. Include a HOW SUPPLIED section.

RECOMMENDATIONS:

A. DMETS does not recommend the use of the proprietary name Vantas.

B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

C. DDMAC finds the proprietary name Vantas acceptable from a promotional perspective.

)METS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

Kristina C. Arnwine, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Denise P. Toyer, PharmD
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Outpatient Written	Inpatient Written	Verbal
Vantas	Vamtas	Vantas
Vantas	Vanta	Vantin
Vantas	Vantas	Vantin
Vantas	Vantas	Vantis
Vantas	Vantas	Vantis
Vantas	Vantas	Vantis
Vantas	Vantas	Vantis
Vantas	Vantas	Vantis
Vantas	Vantas	Vantris
Vantas	Vantas	Vantrix
Vantas	Vantas	Zampres
Vantas	Vantas	
Vantas	Vantas	
Vantas	Vantas	
Vantas	Vantas	
Vantas	Vantas	
Vantas	Vantas	
Vantas	Vantas	
Vantas		
Vantas		
Vantas		
Vantus		

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

/s/

Kristina Arnwine
7/7/04 05:16:12 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
7/7/04 05:18:05 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/7/04 05:28:58 PM
DRUG SAFETY OFFICE REVIEWER

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Division of Surveillance, Research, and Communication Support Technical Support
HFD-410, Parklawn Bldg, Room 6-22
Attention: Leslie Stephens

FROM: Nenita Crisostomo, Project Manager
Division of Reproductive and Urologic Drug Products
Phone: 301-827-7260

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
March 5, 2004		21-732	New NDA	December 12, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Vantas (histrelin acetate implant)	Standard	GnRH agonist	July 5, 2004

NAME OF FIRM: Valera Pharmaceuticals, Inc.

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
- X PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER

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:

This consult is requested by Dr. Mark Hirsch, Urology Team Leader. Attached is a hard copy of the Patient Summary Information and the Insertion and Removal Procedures. The User Fee Goal Date is October 12, 2004. Please call me if you have any questions.

Thank you,
Nita Crisostomo

Cc: Mark Hirsch, Harry Handelsman, Janine Best

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL X HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Director, Division of Drug Marketing, Advertising, and Communication (DDMAC), HFD-42
Parklawn Bldg, Room 17B-17
Attention: Barbara Chong

FROM: Nenita Crisostomo, Project Manager
Division of Reproductive and Urologic Drug Products
Phone: 301-827-7260

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
March 5, 2004		21-732	New NDA	December 12, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Vantas (histrelin acetate implant)	Standard	GnRH agonist	July 5, 2004

NAME OF FIRM: Valera Pharmaceuticals, Inc.

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
- X PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER

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
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- ☐ 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 consult is requested by Dr. Mark Hirsch, Urology Team Leader. Attached is a hard copy of the Physician Insert. The User Fee Goal Date is October 12, 2004. Please call me if you have any questions.

Thank you,
Nita Crisostomo

Cc: Mark Hirsch, Harry Handelsman, Andrew Haffer, Corinne Kulick

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL X HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

14 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Director, Division of Medication Errors and Technical Support, HFD-420
Parklawn, Room 6-34
Attention: Sammie Beam

FROM: Nenita Crisostomo, Project Manager
Division of Reproductive and Urologic Drug Products
Phone: 301-827-7260

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
March 5, 2004		21-732	New NDA	December 12, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Vantas (histrelin acetate implant)	Standard	GnRH agonist	July 5, 2004

NAME OF FIRM: Valera Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
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- ☐ RESUBMISSION
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- ☐ CONTROL SUPPLEMENT
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- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER

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:

This consult is requested by Dr. Mark Hirsch, Urology Team Leader, for the evaluation of the trade name, Vantas (histrelin acetate implant). Attached is a hard copy of the Physician Insert and the container/carton labeling. The User Fee Goal Date is October 12, 2004. Please call me if you have any questions.

Thank you,
Nita Crisostomo

Cc: Mark Hirsch, Harry Handelsman, Su Tran, Carol Holquist

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL X HAND
JRE OF RECEIVER	SIGNATURE OF DELIVERER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: February 24, 2004

To: William B. Gray, M.S. Senior Director of Regulatory Affairs	**From:** Nenita Crisostomo. R.N. Regulatory Project Manager
Company: Valera Pharmaceuticals, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 609-409-1650	**Fax number:** 301-827-4267
Phone number: 609-409-9010 x224	**Phone number:** 301-827-4260

Subject: NDA 21732-Vantas (histrelin acetate) implant--Filing (74-day) Letter

Total no. of pages including cover: 5

Comments:

Document to be mailed: ☑ YES ☐ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

2-24-04

FILING COMMUNICATION

NDA 21-732

Valera Pharmaceuticals, Inc.
Attention: William Gray, M.S.
Senior Director of Regulatory Affairs
8 Clarke Drive
Cranbury, NJ 08512-3617

Dear Mr. Gray:

Please refer to your December 12, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vantas (histrelin acetate) implant.

We also refer to your submission dated December 23, 2003, Serial # 001, containing a revision in Item 1.0, the Index, where Item 3.0 Summary, was initially omitted. Additionally, we also refer to Serial #002 dated February 2, 2004, containing your responses to specific issues discussed during the teleconference with you on January 26, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on February 10, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following review issues and have the following requests for additional information. Our filing review is a preliminary evaluation of the application and is not indicative of all deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Clinical:

1. You report expulsion of the histrelin subdermal implant in 8 patients. Of these 8 patients, 7 had the drug product inserted with trochar #2 (which was manufactured out of a tuberculin syringe) and the other patient who experienced an expulsion had his drug product inserted manually. You hypothesize that the following factors contributed to the expulsions: implantation technique, trochar #2 itself, and post-implantation patient instructions. Further, you state that a well-designed insertion tool, a standardized insertion technique, and a consistent set of patient instructions should decrease the likelihood of expulsions. You support this statement by the absence of expulsions following the introduction of trochar #3 (along with detailed written patient instructions and standardization of the insertion

methodology) on April 2, 2003. Therefore, the issue of implant expulsion will be a major clinical review issue, especially the reason(s) for the expulsions and the proposed methods for reducing the risk of expulsions. Provide any available additional information to support your hypothesis that a well-designed insertion tool (e.g. trochar #3), a standardized insertion technique, and a consistent set of patient instructions will decrease the likelihood of expulsion.

2. In your February 2, 2004, amendment to the original NDA, you stated that a total of 65 patients had the histrelin subdermal implant inserted using trochar #3. You also stated that all of these 65 patients were receiving their *second* subdermal implant in the context of their ongoing participation in Study 301. You further stated that all of these insertions were done on or after April 2, 2003. Of this cohort of 65 patients, a total of 10 patients, 23 patients, 22 patients, 8 patients and 2 patients will reach the end of the year-long treatment period in April, May, June, July, and August of 2004, respectively. Therefore, at the time of the 120-Day Safety Update in April 2004, you expect to provide 7 to 11 months of safety information on these 65 patients. Further, you proposed to provide "relevant summary safety data" on this cohort in monthly sequential NDA amendments beginning in May 2004 and ending in August 2004 (while the NDA is under review). Therefore, the results of and the amount of data you provide to support the safety of the histrelin subdermal implant when implanted with trochar #3 (including standardized insertion methodology and patient instructions) will be a review issue. While you may submit sequential amendments to the NDA as you proposed, the Division will assess each amendment as it is received and will decide upon regulatory action at the time of receipt. When available, submit all available data for those patients who have completed a full 12-month treatment period following implantation with trochar #3. If patients have undergone both insertion and re-implanation with trochar #3, such information should also be submitted. If no such information is available, provide justification for lack of such information and/or your plans to submit such information.

3. You report two patients in whom the subdermal implant could not be located either through direct palpation or through ultrasound localization. In one of these patients, displacement of the implant was only discovered when serum testosterone was noted to rise above castrate level. Therefore, inability to locate the implant following insertion will be a review issue. Provide an explanation for the inability to locate the implant in these cases. You should propose an algorithm for prescribers to follow in the event that an implant cannot be palpated and also in the event an implant cannot be localized using ultrasound.

4. Provide the volume and page numbers of the NDA wherein you have provided the data on the ease or difficulty of the implantation and explantation/re-implantation procedures, as judged by the individual investigator. If available, provide this information separately for trochar #2 (using the pre-April 2, 2003 methodology) and for trochar #3 (using the post-April 2, 2003 methodology).

Chemistry:

Please provide 5 samples of the to-be-marketed implantation kit (trocar and surgical tray).

Clinical Pharmacology

1. Confirm that the formulation used in the Phase 3 clinical evaluation program is the same as the formulation intended to be marketed.
2. If possible, provide electronic study summaries/reports for all the clinical pharmacology and biopharmaceutics related studies. These documents should be sent to the electronic document room, not to the Division directly.

Center for Devices and Radiological Health (CDRH)

1. You have provided the history of how the device has evolved and the manufacturing processes. Provide a description of the **finished** device used in the clinical trial. In the description, include the following: the type of plastic along with a brief narrative description used for each of the multi-pieces used to make the insertion trocar, and the type of stainless steel used to make the cannula.
2. On page 004 and other sections, the use of a button on the device is used to remove the implanter and leave the Histrelin implant under the skin. Provide a brief summary of testing done (bench and clinical) to assure that this feature functions as intended.
3. In Section 4.4.6 you have provided sterilization information including the method [ ] and the dosages that were established to attain the sterility. Provide the Sterility Assurance Level (SAL) and the type of packaging used to maintain the sterility of the device. Was [ ] testing done on the final finished device? Provide only the test results.
4. Provide test results for biocompatibility according to [ ] for the device component that has blood and tissue contact.
5. Device and all package labeling for the final finished product (device) should be provided for review.

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 Nenita Crisostomo, R.N., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation III
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/

Daniel A. Shames
2/24/04 01:53:31 PM

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

REQUEST FOR CONSULTATION

Division/Office): Peter Cooney, Ph.D.
Director, Office of Microbiology (HFD-805)
Room 18B-08

FROM: Nenita Crisostomo, Project Manager
Division of Reproductive and Urologic Drug Products
Phone: 301-827-7260

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 11, 2004		21-732	New NDA	December 12, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Vantas (histrelin acetate implant)	Standard	GnRH agonist	June 11, 2004

NAME OF FIRM: Valera Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
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- ☐ RESUBMISSION
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- ☐ CONTROL SUPPLEMENT
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- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER

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:

Dear Dr. Cooney:

The drug is in a pellet form, [redacted] in a polymer cartridge, and together implanted subcutaneously with an implantation (Trocar) tool. Please evaluate as requested by Dr. Suong Tran, Chemist. Please call me if you have any questions.

Thank you,
Nita Crisostomo

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL X HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Nenita Crisostomo
2/11/04 12:13:50 PM

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21732/000 Sponsor: VALERA

Org Code : 580 8 CLARKE DR

Priority : CRANBURY, NJ 085123617

Stamp Date : 12-DEC-2003 Brand Name : VANTAS (HISTRELIN ACETATE)

PDUFA Date : 12-OCT-2004 50MG IMPLANT

Action Goal : Estab. Name:

District Goal: 13-AUG-2004 Generic Name: HISTRELIN ACETATE

Dosage Form: (DRUG DELIVERY SYSTEM)

Strength : 50 MG

FDA Contacts: N. CRISOSTOMO Project Manager (HFD-580) 301-827-4260

S. TRAN Review Chemist (HFD-580) 301-827-4260

M. RHEE Team Leader (HFD-580) 301-827-4237

Overall Recommendation: ACCEPTABLE on 04-OCT-2004by S. ADAMS (HFD-322) 301-827-9051

Establishment : CFN : FEI : [ ]

[

]

DMF No: AADA:

Responsibilities: [ ]

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-JUN-04

Decision : ACCEPTABLE

on : DISTRICT RECOMMENDATION

Establishment : CFN : [ ] FEI : [ ]

[

]

DMF No: AADA:

Responsibilities: [ ]

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 04-OCT-04

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

[

]

DMF No: AADA:

Responsibilities: [ ]

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

File : NEC OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-JUL-04

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [redacted] FEI : [redacted]

[redacted]

[redacted]

DMF No: [redacted] AADA:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 04-OCT-04

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [redacted] FEI : [redacted]

[redacted]

[redacted]

No: AADA:

Responsibilities: FINISHED DOSAGE STERILIZER

Profile : SSP OAI Status: NONE

Milestone: OC RECOMMENDATION

Milestone Date: 21-JAN-04

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : 2243842 FEI :

VALERA PHARMACUETICALS

8 CLARKE DRIVE

CRANBURY, NJ 08512

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : NEC OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 02-AUG-04

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

NDA 21-732
Vantas™ (histrelin implant)
Valera Pharmaceuticals

METHODS VALIDATION

For the Methods Validation package, the sponsor submitted on August 9, 2004, as requested by the Division, a list of samples to be submitted to FDA labs, with the batch/lot numbers and sample amounts, as well as batch analysis results for these samples. Samples include both the drug product and the drug substance.

The Methods Validation will be requested after approval of this NDA.

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

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

Date: February 09, 2004

From: Viola Hibbard, Nurse Consultant
DAGID/GHDB, HFZ-480

Through: Anthony Watson, Branch Chief, CDRH/ODE/DAGID/GHDB, (HFZ-480)

Subject: Consult Review for NDA 21-732

To: Suong Tran, Ph.D.
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products

CC: Nita Crisostomo, R.N., RPM

I. Introduction

This consult is for CDER to provide a review of a device used for implantation of Vantas (histrelin implant). It is a drug/device combination designed to provide a sustained release of a steady amount of histrelin over a period of one year when implanted subdermally with the trocar device. Vantus™ is indicated in the palliative treatment of advanced prostate cancer.

II. Device Description

The insertion device was developed over time through a number of manual modifications of a tuberculin syringe. The second manual design was used in the clinical trials. A new device was designed for commercialization of this drug/device combination. Valera produced a new trocar/cannula to enhance and improve the previous implanter.

The new trocar/cannula device was designed by [ ] and manufactured by [ ] for Valera. This insertion tool is composed of a multi-piece plastic tool, [ ] The cannula is controlled by a button, which is extended to hold the implant. The implant is inserted in the open end of the cannula. The implanter is inserted under the skin up to the depth line on the cannula. To insert the implant, the thumb pulls the implanter button back, then, the implanter is removed from the insertion site, leaving the Histrelin implant under the skin. The device handle geometry is designed to assure a proper shallow approach, controlled by guiding the cannula subcutaneously and not intramuscularly. The geometry is supposed to assure a handgrip that effectively maintains the back-up piston stationary as the cannula retracts relative to the capsule. This new device was then used by Valera for use in the clinical trial of 66 patients.

The shell, scoop and post of the device are made of [ ] The cannula is made of stainless steel and has a tip protector made of [ ].

III. Consult Review Issues

Consult review questions submitted to CDER on February 9, 2004 for the filing letter.

CDRH Review Issues

1. You have provided the history of how the device has evolved and manufacturing processes. Please provide a description of the **finished** device used in the clinical trial. In the description, please include the following: the type of plastic along with a brief narrative description used for each of the multi-pieces used to make the insertion trocar, and the type of stainless steel used to make the cannula.
2. On page 004 and other sections, the use of a button on the device is used to remove the implanter and leave the Histrelin implant under the skin. Please provide a brief summary of testing done (bench and clinical) to assure that this feature functions as intended.
3. In Section 4.4.6 you have provided sterilization information including the method [ ] and the dosages that were established to attain the sterility. Please provide the Sterility Assurance Level (SAL) and the type of packing used to maintain the sterility of the device. Was [ ] testing done on the final finished device? If so, did that testing show that it has passed the testing?
4. Please provide test results for biocompatibility according to [ ] for the device component that has blood and tissue contact.
5. Device and all package labeling for the final finished product (device) should be provided for review.

IV. Conclusion and Recommendations

A. Bench testing to determine if the device will function as intended.
B. Sterility information to include sterilization method and validation, Sterility Assurance Level (SAL) and Pyrogen test method.
C. Biocompatibility Testing according to ISO 10993.
D. The prescription statement should appear somewhere on the labeling . I do not find this on the package insert or on the device label.

Thank you.

Viola Hibbard, RN., BSN
VSH@CDRH.fda.gov
301-594-1287 X173

12-30-03

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):
Center: Center for Devices and Radiological Health
Division: ODE/DAGID
Mail Code: HF Z 480
Consulting Reviewer Name: Pandu Soprey, Ph.D.
Building/Room #: Corp Rm 340 L
Phone #: 301-594-1287 ext 178
Fax #:
Email Address: sopreyp@cdrh.fda.gov
RPM/CSO Name and Mail Code:

From (Originating Center):
Center: Center for Drug Evaluation and Research
Division: Division of Reproductive and Urologic Drug Products
Mail Code: HFD-580
Requesting Reviewer Name: Suong Tran, Ph.D., Chemist
Building/Room #: Parklawn Bldg, Rm 18B17
Phone#: 301-827-7515
Fax #: 301-827-4267
Email Address: crisostomon@cder.fda.gov
RPM/CSO Name and Mail Code: Nita Crisostomo, R.N. HFD-580
Requesting Reviewer's Concurring Supervisor's Name: Moo Jhong Rhee, CMC Team Leader

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: Dec. 30, 2003

Requested Completion Date: June 30, 2004

Submission/Application Number: NDA 21-732
(Not Barcode Number)

Submission Type: NDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

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

Submission Receipt Date: December 12, 2003

Official Submission Due Date: October 12, 2004

Name of Product: Histrelin Subdermal Implant

Name of Firm: Valera Pharmaceuticals (formerly HydroMed Sciences)

Intended Use: Palliative treatment of advanced prostate cancer

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

1. Volume 5 of 344, containing review documents for the drug product delivery system (Trocar Device)
2. Videotape: "Vantas Implant Video"

Documents to be returned to Requesting Reviewer? ☐ Yes ☑ No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: ☑ Consultative Review ☐ Collaborative Review

Dear Dr. Soprey,

As per our telephone discussion, please review the attached documents with related videotape (implantation demo). Vantas (histrelin implant) is a drug/device combination designed to provide a sustained release of a steady amount of histrelin over a period of one year when implanted subcutaneously with the trocar device. Histrelin was initially approved in 1991 under NDA 19-836 for treatment of central precocious puberty. Related IND 40,772. Our filing meeting is scheduled for January 20, 2004. Please contact me at 301-827-7260, or Dr. Suong Tran at 301-827-7515, if you have any questions. Thank you.

Nita Crisostomo, RPM

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/s/

Nenita Crisostomo
12/30/03 04:45:49 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

12-24-03

NDA 21-732

Valera Pharmaceuticals
Attention: Mr. William Gray
Senior Director of Regulatory Affairs
8 Clarke Drive
Cranbury, NJ 08512-3617

Dear Mr. Gray:

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:	VANTAS ™ (histrelin acetate) 50 mg implant
Review Priority Classification:	Standard
Date of Application:	December 12, 2003
Date of Receipt:	December 12, 2003
Our Reference Number:	NDA 21-732

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 February 10, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 12, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/ Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research, HFD-580
Division of Reproductive and Urologic Drug Products
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
12/24/03 11:08:49 AM
Chief, Project Management Staff

INDUSTRY MEETING MINUTES

Date: August 12, 2003 **Time:** 11: 00 – 12:30 P.M.

Location:	Food and Drug Administration 5600 Fishers Lane Rockville, MD 20857 Parklawn, Chesapeake Conference Room, 3rd Flr.
IND:	40,772
Drug Name:	Histrelin Subdermal Implant
Sponsor:	Hydro Med Sciences (HMS)
Indication:	Palliative treatment of advanced prostate cancer
Type of Meeting:	Pre-NDA
External Participant Lead:	David Tierney, M.D.
Meeting Chair:	Mark Hirsch, M.D.
Meeting Recorder:	Nenita Crisostomo, R.N.

FDA Attendees:
Julie Beitz, Deputy Director, Office of Drug Evaluation III (HFD 103)
Daniel Shames, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Donna Griebel, M.D. - Deputy Director, DRUDP (HFD-580)
Mark Hirsch, M.D. - Medical Team Leader, DRUDP (HFD-580)
Harry Handelsman, M.D - Medical Officer, DRUDP (HFD-580)
Suzanne Thornton, Ph.D., Pharmacologist, Acting Team Leader, DRUDP (HFD-580)
Krishan Raheja, D.V.M., Ph.D. - Pharmacologist, DRUDP (HFD-580)
Ameeta Parekh, Ph.D.— Pharmacokinetics Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Sayed Al-Habet, Ph.D. –Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Suong Tran, Ph.D. – Chemist, DNDC II @ DRUDP (HFD-580)
Mike Welch, Ph.D., Biostatistics Team Leader, Division of Biometrics II, (HFD-715)
James McVey, M.S. – Microbiologist, Office of Pharmaceutical Science, (HFN-805)
Patricia Cricenti, Ph.D. – Chief, General Hospital Devices Branch, Center for Devices and Radiological Health (CDRH), (HFZ-480)
Nenita Crisostomo, R.N. – Regulatory Project Manager. DRUDP (HFD-580)

External Attendees:
David Tierney, M.D.—President and CEO Hydro Med Sciences

External Attendees *(continued):*
Petr Kůzma, M.S.—Vice-President, Research and Development, Hydro Med Sciences
William Gray, M.S.—Senior Director Regulatory Affairs, Hydro Med Sciences
Lara Wilt, B.A.—Quality Assurance Manager, Hydro Med Sciences
[ ] -Clinical Consultant,
[ ]
Martin Dineen, M.D.—Principal Investigator, Atlantic Urological Associates
[ ]
[ ]
Frank Sasinowski, J.D.—Consultant, Hyman, Phelps & McNamara, P.C.

Background: An investigational new drug (IND), Histrelin Subdermal Implant, is being developed by Hydro Med Sciences. A pre-new drug application (pre-NDA) meeting with the Agency was requested to discuss the content and format of the upcoming NDA. Histrelin was originally approved (under NDA 19-836, 1991) for treatment of central precocious puberty. Histrelin is a hydrogel implant containing 50 mg of histrelin acetate, a synthetic nonpeptide gonadotropin-releasing hormone (GnRH) agonist for the palliative treatment of advanced prostate cancer. The implant is designed to provide sustained delivery of histrelin for one year. Phase 3 study in approximately 140 prostate cancer patients is expected to be completed by the end of August 2003. Submission of the NDA is planned for November 2003.

PRESENTATION: The sponsor presented the following:
- Brief description of the Histrelin Subdermal Implant
    - The sponsor presented a sample of the hollow, cylindrical polymeric hydrogel implants containing histrelin acetate pellets
    - Implantation Tool, manufactured by Hydro Med Sciences specifically for the subdermal implantation of histrelin. Videotape of the procedure was provided by the sponsor.
- Chemistry and Manufacturing
- Pre-Clinical Data
- Clinical Data

QUESTIONS FOR DISCUSSION

Question 1: Does the Division agree with the decision not to quantify histrelin urine concentration measurements in RHI subgroup of the phase 3 study?

FDA Response: Yes.

Question 2: Does the Division regard the proposal of HMS for describing the ADME of histrelin in humans satisfactory?

FDA Response: The sponsor's proposal for conducting ADME study in 6 subjects after IV administration of 500 mcg dose is acceptable. (However, during the meeting, the sponsor

proposed to conduct a subcutaneous study, and not an IV study. In regard to this proposal, please refer to additional comments below, under *Clinical Pharmacology and Biopharmaceutics.*)

Question 3: Does the Division regard the IVIVC information proposed sufficient for future bio-waiver? If not, what IVIVC information would be necessary for this type of technology?

FDA Response: The sponsor's approach to developing IVIVC for such products seems appropriate. Because you have not made a change in the to-be-marketed formulation and you are considering this for future references, please provide complete details and a proposal in the NDA submission for our specific comments.

Question 4: Does the Division have any concerns regarding proposed dossier content for the clinical Pharmacology and Biopharmaceutics of histrelin?

FDA Response: This is acceptable.

Question 5: Is the proposed Table of Contents and format acceptable for submission?

FDA Response: No, we need an additional full section in the ISS on extrusions/expulsions/implant losses and information on local site tolerability. We also need information on the insertion and removal technique—how to do it, ease of procedure, complications, etc.

Question 6: Currently, no method of imputation for patients with missing testosterone values at weeks 4 or 52 has been discussed with the FDA. Patients who withdraw from the study due to uncontrolled testosterone levels or an adverse event ascribed to be related to the Histrelin Subdermal implant will be classified as treatment failures. Patients who withdraw from the trial for any other non-disease or non-treatment related issues will be included in the analyses up until the point of discontinuation and excluded from the analysis once off study. Given inferential statistics will be used to assess efficacy, coupled with the stringent bounds for assessing response, excluding patients will not be without consequence by increasing the length of the confidence limit. Is this methodology acceptable?

FDA Response:

1. Patients with missing serum T at week 4 or at week 52 should be excluded from the "completer analysis" (the preferred analysis for the label). However, each patient's data will be assessed carefully and if just the week 52 is missing and non-castrate, that patient could be a responder.
2. If a patient drops out, that patient also should be excluded from the "completer analysis". However, if his last T prior to withdrawal was castrate, he won't be counted as a "non-responder". One caveat and still to be decided is the issue of how to count extrusions/infections or implant losses.

By strict standards, patients with expulsion or implant loss are not to be counted as "completers". However, if the number of such patients is large, this will be a review issue. The Division will conduct its own secondary analyses where (a) these patients are all treated as efficacy failures, and (b) those that are replaced and remain per protocol are successes but the rest are failures.

ADDITIONAL COMMENTS

Center for Devices and Radiological Health (CDRH):

Agency: Explain how the implant is inserted into the patient—this is not included in the submission.

Sponsor: A slit is made through the skin, the pellet is then guided with the implantation tool for insertion subcutaneously, and then the slit is closed with sutures. The tool helps to keep the pellet in and thus far, the sponsor has not seen any expulsions with the novel implantation tool. However, the sponsor explained that the former device, a modified insulin needle, had problems.

Agency: Is the tool approved for use? Who developed the tool and will it be marketed with the drug? Is there a protocol amendment about the device?

Sponsor: The tool was developed and planned to be marketed by the sponsor; however, it has not been approved by the Agency. There was no protocol amendment about the device.

Agency: Information about the implantation tool must be included in the submission. A portion of the NDA should be dedicated to the tool so that it may be easily extracted for review by CDRH. The tool needs to be approved. This will be a major review issue.

Microbiology:

- The references cited for [ ] are not used for drugs. Refer to the 1984 Guidance for Industry for the Submission Documentation for Sterilization Process Validation in applications for Human and Veterinary Drug Products. This may be found in the Guidance section of the CDER website (a copy is provided for the meeting).
- The ample opportunity for microbial incorporation and growth must be addressed in the application. Provide the in-process steps that are taken to avoid contamination. Provide the specifications used for [ ] bio-burden.
- If the applicant decides to use the endotoxin test instead of the rabbit pyrogen test, provide the maximum human dose used and the maximum valid dilution. Provide the working dilution for routine assay.
- A container/closure test will be required as part of product development. Once validated, no further closure testing will be required unless one of the components is changed.
- The proposed contents section (p.55) does not appear to have a section for Product Microbiology. It should follow the CMC section. If Section 7 is the section which will

contain the microbial control and sterilization validation information, it should be moved to follow Section 3.

Chemistry: The chemistry review provided some comments at the meeting. Additional detailed comments are also provided herein.

- Include a device information package in the NDA for a consult review by CDRH.
- Include a sterilization validation package in the NDA for a consult review by the Microbiology team.
- Referring to the proposed NDA table of content in section 10 of the meeting package, include Control of Excipients in Chemistry, Manufacturing, and Controls.
- Include the drug substance specification in the NDA. The specification in the NDA should indicate the tests that the drug product manufacturer will routinely perform. At a minimum, the drug product manufacturer should confirm the identity of a drug substance batch as well as its assay and impurity values.
- The drug substance specification in the NDA should include [ ] and a note that this test is implemented by the drug product manufacturer.
- Discuss the effects of the drug substance [ ] on the elution rate of the drug product as part of the justification for the proposed [ ] criteria of [ ]
- For the drug product, indicate the compendial status or quality grade of the components as well as the biological source of stearic acid.
- List all the components [ ] of the polymer cartridge.
- Perform a stability study to show that the [ ] step of the implant does not adversely affect the active ingredient.
- Confirm the following study described in the 9-SEP-1999 amendment to the IND: a study to evaluate the effects of the sterilization process on the active ingredient, cartridge dimensions and weight, and extractables/leachables from the cartridge, vial, and closure.
- Include the following in the drug product specification: [ ]
- Stability data show that there is a migration of the drug substance to the surface of the cartridge. This accumulation results in an initial elution rate (Week 1 data) that is higher than subsequent elution rates (Weeks 3 and 4 data). Therefore, Elution Rate testing and acceptance criteria should include Day 1 for both release and stability testing. The Elution Rate criteria on Day 1 should take into account both the safety limits (i.e., maximum daily exposure) and the stability data (i.e., maximum elution rate on Day 1 for implants that reach the expiration date).
- The sponsor was asked if there is any effect on the stability of the drug, which is partially immersed in the saline solution, if the container is placed in different positions (e.g., upside down, horizontally). The sponsor denied any effects and will provide the data.
- The proposed Elution Rate range of [ ] µg is too wide. The criteria should be tightened to reflect release and stability data.

- Elution Rate should include the following acceptance criteria :
  - [redacted]
  - [redacted]
  - [redacted]
- List Degradation and Impurity Products as follows in the release and stability specifications:
  Each specified and identified,
  Each specified and unidentified,
  Each unspecified, and
  Total Impurities.
- For Degradation and Impurity Products, the proposed reporting threshold of [redacted] is acceptable. In addition, any impurity/degradant greater than [redacted] should be identified and qualified. Each unspecified impurity should be NMT [redacted]
- The stability data for the three primary batches (Phase 3 clinical batches) 508, 510, and 511 only have Total Impurities listed. Degradation data should include levels of the specified and identified impurities, specified and unidentified, unspecified, and Total Impurities.
- Provide stability data to support any storage of the polymer cartridges, histrelin pellets, assembled implants, and hydrated implants beyond [redacted] days.
- Provide stability data [redacted] for the drug product stored under conditions equivalent to 1-year in vivo conditions.

Pharmacology/Toxicology:

- The original NDA 19-836 was approved in 1991 and withdrawn in December 2002 by Shire Pharmaceutical Development, Inc. The sponsor agreed to provide the Right of Reference to the pre-clinical studies conducted by the original NDA sponsor and if requested by the Agency, they can provide the volumes of data from these studies.
- If HMS has the right of reference, then we will need additional new toxicity information only on one of the three excipients, TMP-TMA, which is being used for the first time. Limit dose is specified in ICH Guidelines. Please refer to these guidelines for genotoxicity requirements.
- If HMS **does not** have right of reference, then you will have to support the pre-clinical requirements; i.e., literature citation.
- The submission type [whether it's a 505 (B) 1 or 505 (B) 2] will be discussed when the NDA submission is received.
- There may be additional toxicology studies required depending on the results of cartridge stability testing.

Clinical:

- Submit narration of case report form of all patients that dropped-out of the study, including the eight patients who dropped-out "at their own request". It is especially concerning that

seven dropped-out at 40 weeks into the study. Include serum testosterone levels in all patients prior to withdrawal.

- Expulsions of the implant will be a review issue.
    - Explain how efficacy assessment is impacted by the expulsions.
    - Provide the reasons for the expulsions.
    - Include a unique section in both the ISS and ISE on extrusions/expulsions/implant losses.
- Explain the procedures taken when an implant can not be found at the implantation site.
- Explain how to count Patient 37/1032 ("compassionate use") in the data analysis.
- In the NDA, include the following:
    - Procedure on subcutaneous insertion
    - Include surgical technique utilized, i.e. piercing of insertion site, depth of incision, width of suture opening, etc.
    - Provide the pre- and post-op assessments, i.e. description of insertion site during the insertion process, periodic assessments (if any), and after one year (before/after removal of the implant), etc.
- Explain each adverse event, including those described as "independent".
- For the efficacy analysis, there should be one single primary endpoint: attaining castration by Day 28 and maintaining castration through 52 weeks.
- Provide training/educational materials as part of NDA: physician insert, patient package insert, training video.
- The Division would like to see efficacy data on "conversion" in at least 50 patients who reach week 52 and are then re-implanted.

The Agency agreed to sponsor's request to integrate the statistical and clinical sections together in the NDA.

Clinical Pharmacology and Biopharmaceutics:

- For all explantations, provide the measurement of the amount of remaining drug, if available.
- Provide the data for the testosterone as well as drug levels if obtained before and after explantations. For the second administration of the drug, provide plasma concentrations of drug as well as testosterone, if available. Similar data should also be provided for the dose proportionality/dose finding study.
- The sponsor stated that unlike previously proposed, an absolute bioavailability study will not be conducted; instead, a single dose of a solution will be subcutaneously administered and ADME will be attempted with this study; the sponsor was advised that a RIA assay may have cross reactivity and that consideration should be given to its specificity limitations to address ADME. If the sponsor chooses, the protocol may be provided for our review.
- In addition to the information proposed by the sponsor, the sponsor should also address in-vitro release profiles and specification, formulation details, metabolism and drug interaction potential, special population PK data (e.g. hepatic and renal patients) and the ADME information in the Clinical Pharmacology and Biopharmaceutics Section of the NDA.

Signature: Meeting Chair

{See Appended Electronic Signature}

Mark Hirsch, M.D.

Note to Sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcome.

Cc:
HFD-580/Division Files
HFD-580/Original IND
HFD-580/dshames, mkober, hhandelsman,kraheja, sthornton, stran, mrhee, aparekh, sal-habet, ncrisostomo

Created by: Nenita Crisostomo, 8/8/03, 8/13/03
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/s/

Mark S. Hirsch
9/22/03 05:51:45 PM

Teleconference Minutes

Date: December 19, 2001 **Time:** 1:00-2:00 PM **Location:** Parklawn; 17B-43

IND 40,772 **Drug:** Histrelin Subdermal Implant

Indication: palliative treatment of advanced prostate cancer

Sponsor: Hydro Med Sciences (HMS)

Type of Meeting: Guidance

Meeting Chair: Mark Hirsch, M.D.

External Lead: David Tierney, M.D.

Meeting Recorder: Jeanine Best, M.S.N., R.N.

FDA Attendees:
Mark Hirsch, M.D., Urology Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Scott Monroe, M.D., Medical Officer, DRUDP (HFD-580)
Kate Meaker, M.S., Statistician, Division Of Biometrics II (DBII) @ DRUDP (HFD-580)
Jeanine Best, M.S.N., R.N., Senior Regulatory Associate

External Participants:
David Tierney, M.D., President and CEO, Hydro Med Sciences
Petr Kuzma, VP, Research and Development, Hydro Med Sciences
Renee King, QA/RA Manager, Hydro Med Sciences
Brenda McCalister-Afflick, Project manager,
Stephen Solomon, Ph.D., Associate Director of Biostatistics,
[ ]
Frank J. Sasinowski, Esq., Regulatory Consultant, Hyman, Phelps, and McNamara, P.C.

Meeting Objective: To provide guidance regarding the sponsor's revised Phase 3 protocol regarding completion and statistical analysis of the data.

Background:
The Histrelin Subdermal Implant is a hydrogel implant containing 50 mg of histrelin acetate, a synthetic nonapeptide agonist for the palliative treatment of advanced prostate cancer. IND 40,772 was submitted to the Agency on October 2, 1992, and has undergone several sponsorship changes since the time of the initial submission. The current sponsor, Hydro Med Sciences (HMS) has been the manufacturer of the histrelin implant since the filing of the IND. HMS assumed sponsor ship of the IND while the agreed upon Phase 3 protocols were underway. The studies were halted prior to the change in sponsorship and HMS is now seeking Agency Guidance for protocol revisions in order to progress with their drug development plans.

Discussion:
Questions
Clinical

1. HMS intends to rely on agreements and discussions between the Division and previous IND sponsors, including the End-of-Phase 2 meeting minutes and subsequent correspondence. Does FDA agree with this approach?

- the Division will make every attempt to keep agreements made at the End-of-Phase 2 Meeting and in subsequent correspondence, but the Division must be provided a list from the sponsor, of the agreements made, before this question can be completely answered

2. Does FDA agree with HMS's approach to revise Protocols 301 and 302 to eliminate the comparitor arm and determine efficacy by pre-specified success proportions and confidence intervals for chemical castration (< 50 ng/dL or 1.75 nmol/L)?

- Study 302 should be used as supportive data towards an NDA containing revised Protocol 301 as a single pivotal trial
- it is acceptable to reopen enrollment in Study 301 and amend the protocol with the proposed modifications including elimination of the comparitor arm; the specific protocol revisions will need to be reviewed for acceptability
- the pre-specified success proportions will need to be defined as well as specifying confidence intervals; the co-primary endpoint should be:
    - the achievement of castration by 4 weeks (A)
    - the maintenance of castration through week 52 (B)
- the usual lower bound of the confidence interval for A should be 90% and the Division recommends a lower bound of 86% for B
- a 2-sided, 95% confidence interval is required

3. Does FDA agree that there will be sufficient subjects enrolled in the combined clinical studies for filing an NDA, assuming that an additional eighty subjects enroll and complete HMS's revised Study 301?

- the Division proposes that Study 301 be the single primary trial submitted for efficacy in the NDA; Study 302 will be used as supportive data to the NDA
- the number of subjects required for the efficacy data will depend on sample size calculations based on the point estimates selected for the co-primary endpoints
- the Division requests 120 patients exposed to the product for 12 months for the safety evaluation; data from Study 302 can contribute to the N for the safety evaluation; it is important to have safety data through week 60 on as many patients as possible to look at data on removal and reinsertion; the sponsor reported that they will have at least 100 patients exposed for 60 weeks; not all of these patients will have the requested PK data because about 53 patients have already completed Week 60 without having the assessments; this is considered acceptable
- the Division requests obtaining samples for serum testosterone (T) and histrelin levels at 48 to 72 hours, at 1 week, at 4 weeks, and at 8 weeks after reinsertion in at least 50 patients; it is important to determine (a) if there is an increase in serum T at the time of reinsertion , and (b), that serum T levels remain suppressed $\leq$ 50ng/dL after reinsertion (i.e., study Weeks 52-60); the 20 patient detailed PK analysis at the time of reinsertion is not required; the 20 patient detailed PK/PD sampling and analysis at initial insertion is required and will be sufficient

Statistical Plan

1. Does FDA agree with the draft Statistical Analysis Plan for combining data from the clinical studies? What additional analysis is recommended?

- refer to the answers to the above questions
- drop-outs must be pre-defined; if a patient drops-out during the trial with T levels suppressed at castrate levels, the patient would not be considered a failure or success, and would drop out of the denominator and numerator for the efficacy evaluation; if a patient is not castrate at time of drop-out, then he would be considered a failure; the sponsor should provide a section in their revised protocol amendment, accounting for drop-outs due to Adverse Events, including the need to remove the implant or spontaneous loss of the implant

Decisions made:

- the revised Study 301 will be the single, Phase 3 trial used for the efficacy evaluation in the NDA submission
- Study 302 and Phase 2 data will be used as supportive data (both efficacy and safety) for the NDA submission
- Study 301 will be a single-arm (histrelin) trial with 2 co-primary endpoints:
  - endpoint A will be the rate of achievement of castration (T levels $\leq$ 50 ng/dL) at 4 weeks
    - the lower bound of the confidence interval will be > 90.0 %
  - endpoint B will be the rate of maintenance of castration through 52 weeks
    - the lower bound of the confidence interval will be no lower than 86.0 %
- 120 patients exposed to the product for 12 months will be required for the safety evaluation in the NDA submission, and at least 50 of these patients from the revised protocol will have the additional PK/PD data after reinsertion of the implant (i.e., serum T levels and serum histrelin levels at 48-72 hours, week 1, week 4, and week 8 after reinsertion)
- for dropouts:
  - patients that drop-out secondary to Adverse Events or other non-drug related issues will not be counted in the primary efficacy analysis
  - patients that drop-out secondary to Adverse Events that are related to the implant or study drug will be analyzed as failures in a secondary analysis
  - a secondary analysis also will be performed for events related to expulsion of the implant

Action Items:

- sponsor will submit the revised protocol for Study 301, as well as the revised statistical plan, as an IND amendment for review
- Meeting Minutes to the sponsor within 30 days

Minutes Preparer **Concurrence, Chair**

Note to Sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

cc:
Original IND
HFD-580/DivFile
HFD-580/PM/Best
HFD-580/Hirsch/Monroe/Meaker

drafted:JAB/December 19, 2001
concurrence:Hirsch,12.20.01/Meaker,12.21.01/Monroe,12.24.01
final:JAB/January 2, 2002

MEETING MINUTES

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

/s/

Jeanine Best
1/2/02 10:00:46 AM
CSO

Mark S. Hirsch
1/3/02 06:28:50 PM
MEDICAL OFFICER

NDA 21-732
Vantas™ (histrelin implant)
Valera Pharmaceuticals

SUMMARY REVIEW-DIVISION DIRECTOR

See Medical Team Leader Memo.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS
Valera Pharmaceuticals, Inc.
8 Clarke Drive
Cranbury, NJ 08512

2. TELEPHONE NUMBER *(Include Area Code)*
(609) 409 9010

3. PRODUCT NAME
histrelin subdermal implant

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
21-732

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER
4682

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?
☐ YES ☒ NO
(See Item 8, reverse side if answered YES)

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and

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Rockville, MD 20852

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Daniel Hayes Daniel J Hayes	Director of Finance and Administration	12/9/03

FORM FDA 3397 (1/03)

Valera Copy

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Delaware

The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AMENDMENT OF "HYDRO MED SCIENCES, INC.", CHANGING ITS NAME FROM "HYDRO MED SCIENCES, INC." TO "VALERA PHARMACEUTICALS, INC.", FILED IN THIS OFFICE ON THE FIRST DAY OF JULY, A.D. 2003, AT 10 O'CLOCK A.M.

A FILED COPY OF THIS CERTIFICATE HAS BEEN FORWARDED TO THE NEW CASTLE COUNTY RECORDER OF DEEDS.

3236297 8100

030433393

Harriet Smith Windsor

Harriet Smith Windsor, Secretary of State

AUTHENTICATION: 2508433

DATE: 07-02-03

CERTIFICATE OF AMENDMENT TO THE AMENDED AND RESTATED CERTIFICATE OF INCORPORATION OF HYDRO MED SCIENCES, INC.

HYDRO MED SCIENCES, INC. (the "Corporation"), a corporation organized and existing under and by virtue of the General Corporation Law of the State of Delaware, does hereby certify:

FIRST: That the Board of Directors of the Corporation, by consent given at a meeting of the Board, said minutes filed with the minutes of proceedings of the Board, duly adopted a resolution declaring advisable the amendment of the Amended and Restated Certificate of Incorporation of the Corporation and submitting the same to the stockholders of the Corporation for approval. The resolution setting forth the proposed amendment is as follows:

> RESOLVED, that subject to the approval of the stockholders of the Corporation, Article 1. of the Amended and Restated Certificate of Incorporation of the Corporation be amended by deleting the existing Article 1. and substituting the following in its place:
>
> "1. The name of the Corporation is Valera Pharmaceuticals, Inc."

SECOND: That a majority of stockholders of the Corporation required to approve the change of name duly consented in writing to the aforesaid amendment in accordance with the provisions of Section 228 of the Delaware General Corporation Law ("DGCL").

THIRD: That the amendment was duly adopted in accordance with the provisions of Section 242 of the DGCL.

IN WITNESS WHEREOF, Hydro Med Sciences, Inc. has caused this certificate to be signed by David Tierney, its President, this 1st day of July, 2003.

HYDRO MED SCIENCES, INC.

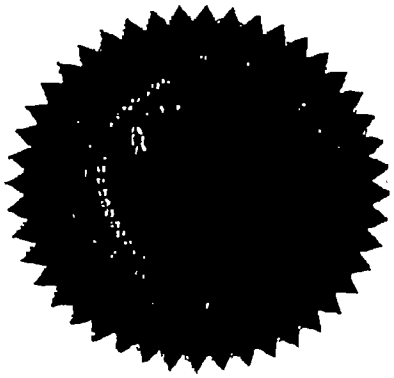
By: _____
David Tierney
President

STATE OF NEW JERSEY
DEPARTMENT OF TREASURY
AMENDED CERTIFICATE OF AUTHORITY

VALERA PHARMACEUTICALS, INC.
With the Previous or Alternate Name
HYDRO MED SCIENCES, INC.

I, the Treasurer of the State of New Jersey, do hereby certify, that the above-named Delaware Foreign Profit Corporation did on the 28th of July, 2003, file and record in this department a name change amendment as by the statutes of this State required.

IN TESTIMONY WHEREOF, I have hereunto set my hand and affixed my Official Seal at Trenton, this 29th day of July, 2003



John E McCormac, CPA
Acting State Treasurer

HYDRO MED SCIENCES, INC. • 8 Clarke Drive • Cranbury, NJ 08512 • Tel: (609) 409-9010 • www.hydromed.com

007038

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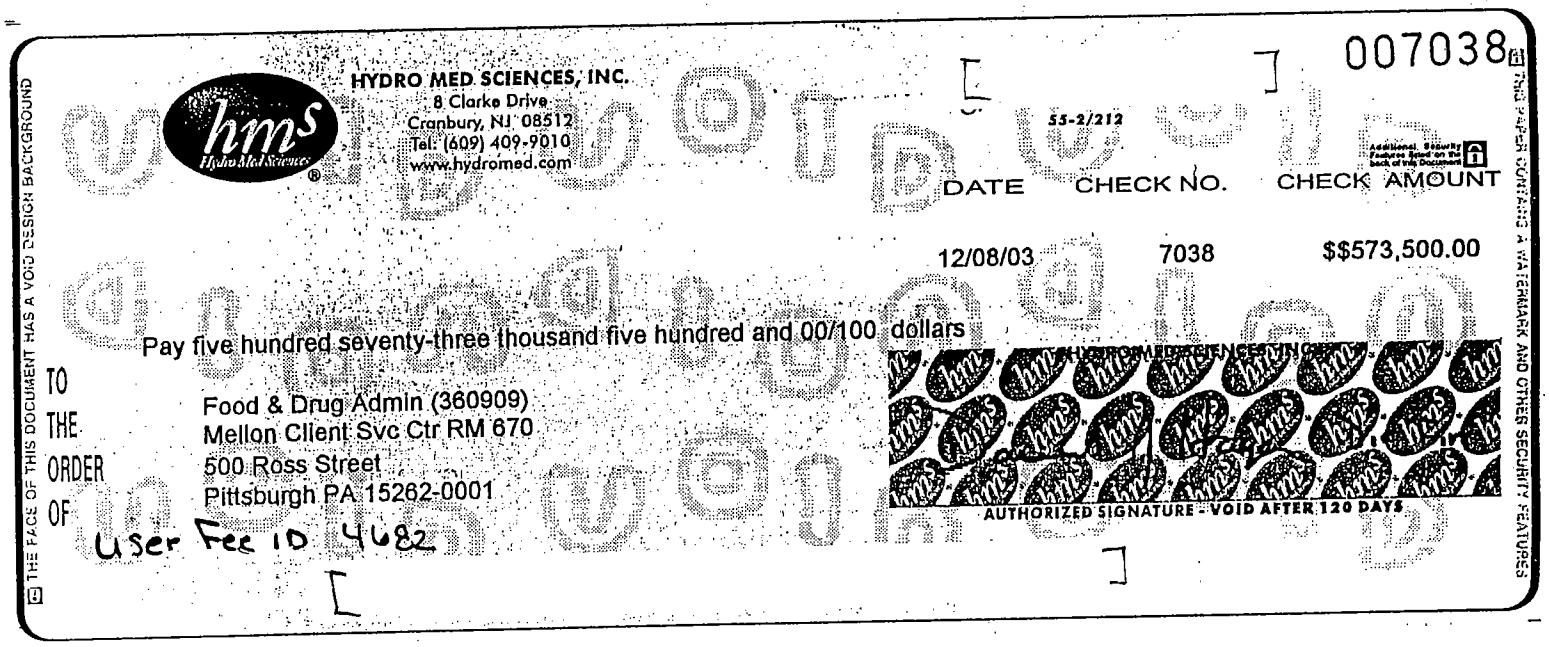
USEFEE468	12/08/03	User Fee ID: 4682	573500.00	0.00	573500.00
			Gross	Discount	Check Amount
Check #	Date	Totals ->	573500.00	0.00	573500.00
7038	12/08/03				



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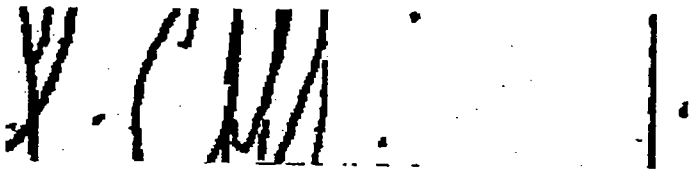

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