CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-044

Administrative/Correspondence Reviews

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

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

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

NDA NUMBER
21-044

NAME OF APPLICANT / NDA HOLDER
Purdue Pharma L.P.

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)
Palladone™ (hydromorphone hydrochloride extended- release) Capsules

ACTIVE INGREDIENT(S)	STRENGTH(S)
hydromorphone hydrochloride	12, 16, 24 and 32 mg

DOSAGE FORM
capsules (extended release)

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
5,958,452	9/28/1999	11/4/2014

d. Name of Patent Owner
Euro-Celtique S.A.

Address *(of Patent Owner)*
122 Boulevard de la Petrusse

City/State
L-2330 Luxembourg

ZIP Code	FAX Number *(if available)*
	44-207-408-0714
Telephone Number	**E-Mail Address *(if available)***
44-207-493-3842	

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)

☞ Philip C. Strassburger, Esq.

Address *(of agent or representative named in 1.e.)*
Purdue Pharma L.P.
One Stamford Forum

City/State
Stamford, CT

ZIP Code	FAX Number *(if available)*
06901-3431	(203) 588-6391
Telephone Number	**E-Mail Address *(if available)***
(203) 588-7639	philip.strassburger@pharma.com

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

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

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

2. Drug Substance (Active Ingredient)

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

3. Drug Product (Composition/Formulation)

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

4. Method of Use

Sponsors must submit the information in section 4 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

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
Philip C. Strassburger CSPTO Reg. No. 34,258	Sept. 13, 2009

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 Philip C. Strassburger, Esq.	
Address Purdue Pharma L.P. One Stamford Forum	City/State Stamford, CT
ZIP Code 06901-3431	Telephone Number (203) 588-7639
FAX Number *(if available)* (203) 588-6391	E-Mail Address *(if available)* philip.strassburger@pharma.com

Department of Health and Human Services
Food and Drug Administration

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TRADE NAME (OR PROPOSED TRADE NAME)
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ACTIVE INGREDIENT(S)	STRENGTH(S)
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DOSAGE FORM
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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,965,161	10/12/1999	11/4/2014

d. Name of Patent Owner	Address *(of Patent Owner)*	
Euro-Celtique S.A.	122 Boulevard de la Petrusse	
	City/State: L-2330 Luxembourg	
	ZIP Code	FAX Number *(if available)*: 44-207-408-0714
	Telephone Number: 44-207-493-3842	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
☞ Philip C. Strassburger, Esq.	Purdue Pharma L.P. One Stamford Forum	
	City/State: Stamford, CT	
	ZIP Code: 06901-3431	FAX Number *(if available)*: (203) 588-6391
	Telephone Number: (203) 588-7639	E-Mail Address *(if available)*: philip.strassburger@pharma.com

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.

Drug Substance (Active Ingredient)

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

3. Drug Product (Composition/Formulation)

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

4. Method of Use

Sponsors must submit the information in section 4 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)* 18, 64, 65, 66	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.)* Management of persistent, moderate to severe pain in patients requiring continuous, around-the-clock analgesia with a high potency opioid for an extended period of time generally weeks to months or longer.	

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

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Philip C. Strassburger USPTO Reg No. 34,258	Sept 13, 2004

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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 Philip C. Strassburger, Esq.	
Address Purdue Pharma L.P. One Stamford Forum	City/State Stamford, CT
ZIP Code 06901-3431	Telephone Number (203) 588-7639
FAX Number *(if available)* (203) 588-6391	E-Mail Address *(if available)* philip.strassburger@pharma.com

Department of Health and Human Services
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TRADE NAME (OR PROPOSED TRADE NAME)
Palladone™ (hydromorphone hydrochloride extended- release) Capsules

ACTIVE INGREDIENT(S)	STRENGTH(S)
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DOSAGE FORM
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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,968,551	10/19/1999	Dec. 24, 2011

d. Name of Patent Owner
Purdue Pharma L.P.

Address *(of Patent Owner)*
One Stamford Forum

City/State
Stamford, CT

ZIP Code	FAX Number *(if available)*
06901-3431	(203) 588-6391
Telephone Number	**E-Mail Address *(if available)***
(203) 588-8000	

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)

Philip C. Strassburger, Esq.

Address *(of agent or representative named in 1.e.)*
Purdue Pharma L.P.
One Stamford Forum

City/State
Stamford, CT

ZIP Code	FAX Number *(if available)*
06901-3431	(203) 588-6391
Telephone Number	**E-Mail Address *(if available)***
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f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

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Drug Substance (Active Ingredient)

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

3. Drug Product (Composition/Formulation)

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

4. Method of Use

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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.)*	

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☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Philip C. Strassburger, Esq.	
Address Purdue Pharma L.P. One Stamford Forum	City/State Stamford,CT
ZIP Code 06901-3431	Telephone Number 203) 588-7639
FAX Number *(if available)* (203) 588-6391	E-Mail Address *(if available)* philip.strassburger@pharma.com

Department of Health and Human Services
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a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,294,195	9/25/2001	12/24/2011

d. Name of Patent Owner	Address *(of Patent Owner)*	
Purdue Pharma L.P.	One Stamford Forum	
	City/State: Stamford, CT	
	ZIP Code: 06901-3431	FAX Number *(if available)*: (203) 588-6391
	Telephone Number: (203) 588-8000	E-Mail Address *(if available)*:

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
☞ Philip C. Strassburger, Esq.	Purdue Pharma L.P. One Stamford Forum	
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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)

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 which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

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

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

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Philip C. Strassburger, Esq. Reg. No. 34,258	Sept. 13, 2004

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 Philip C. Strassburger, Esq.	
Address Purdue Pharma L.P. One Stamford Forum	City/State Stamford, CT
ZIP Code 06901-3431	Telephone Number (203) 588-7639
FAX Number *(if available)* (203) 588-6391	E-Mail Address *(if available)* philip.strassburger@pharma.com

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
21-044

NAME OF APPLICANT / NDA HOLDER
Purdue Pharma L.P.

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)
Palladone™ (hydromorphone hydrochloride extended- release) Capsules

ACTIVE INGREDIENT(S)	STRENGTH(S)
hydromorphone hydrochloride	12, 16, 24 and 32 mg

DOSAGE FORM
capsules (extended release)

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
6,335,033	1/1/2002	Nov. 4, 2014

d. Name of Patent Owner	Address *(of Patent Owner)*	
Euro-Celtique S.A.	122 Boulevard de la Petrusse	
	City/State: L-2330 Luxembourg	
	ZIP Code	FAX Number *(if available)*: 44-207-408-0714
	Telephone Number: 44-207-493-3842	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
Philip C. Strassburger, Esq.	Purdue Pharma L.P. One Stamford Forum	
	City/State: Stamford, CT	
	ZIP Code: 06901-3431	FAX Number *(if available)*: (203) 588-6391
	Telephone Number: (203) 588-7639	E-Mail Address *(if available)*: philip.strassburger@pharma.com

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

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

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

2. Drug Substance (Active Ingredient)

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

3. Drug Product (Composition/Formulation)

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

4. Method of Use

Sponsors must submit the information in section 4 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)* 2, 30, 31	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.)* Management of persistent, moderate to severe pain in patients requiring continuous, around-the-clock analgesia with a high potency opioid for an extended period of time generally weeks to months or longer.	

5. No Relevant Patents

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

6. Declaration Certification

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

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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
Philip C. Strassburger USPTO Reg. No. 34,258	Sept. 13, 2004

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 Philip C. Strassburger, Esq.	
Address Purdue Pharma L.P. One Stamford Forum	City/State Stamford, CT
ZIP Code 06901-3431	Telephone Number (203) 588-7639
FAX Number *(if available)* (203) 588-6391	E-Mail Address *(if available)* philip.strassburger@pharma.com

PSC Media Arts (301) 443-1090 EF

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
21-044

NAME OF APPLICANT / NDA HOLDER
Purdue Pharma L.P.

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)
Palladone™ (hydromorphone hydrochloride extended- release) Capsules

ACTIVE INGREDIENT(S)	STRENGTH(S)
hydromorphone hydrochloride	12, 16, 24 and 32 mg

DOSAGE FORM
capsules (extended release)

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
6,706,281	3/16/2004	11/4/2014

d. Name of Patent Owner	Address *(of Patent Owner)*	
Euro-Celtique S.A.	122 Boulevard de la Petrusse	
	City/State: L-2330 Luxembourg	
	ZIP Code	FAX Number *(if available)*: 44-207-408-0714
	Telephone Number: 44-207-493-3842	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
☞ Philip C. Strassburger, Esq.	Purdue Pharma L.P. One Stamford Forum	
	City/State: Stamford, CT	
	ZIP Code: 06901-3431	FAX Number *(if available)*: (203) 588-6391
	Telephone Number: (203) 588-7639	E-Mail Address *(if available)*: philip.strassburger@pharma.com

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

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

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

2. Drug Substance (Active Ingredient)

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

3. Drug Product (Composition/Formulation)

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

4. Method of Use

Sponsors must submit the information in section 4 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)*: 30 — 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.)*

Management of persistent, moderate to severe pain in patients requiring continuous, around-the-clock analgesia with a high potency opioid for an extended period of time generally weeks to months or longer.

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
Philip C. Strassburger USPTO Reg No. 34,258	Sept 13, 2004

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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 Philip C.Strassburger, Esq.	
Address Purdue Pharma L.P. One Stamford Forum	City/State Stamford, CT
ZIP Code 06901-3431	Telephone Number (203) 588-7639
FAX Number *(if available)* (203) 588-6391	E-Mail Address *(if available)* philip.strassburger@pharma.com

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
21-044

NAME OF APPLICANT / NDA HOLDER
Purdue Pharma L.P.

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)
Palladone™ (hydromorphone hydrochloride extended- release) Capsules

ACTIVE INGREDIENT(S)	STRENGTH(S)
hydromorphone hydrochloride	12, 16, 24 and 32 mg

DOSAGE FORM
capsules (extended release)

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.

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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
6,743,442	6/1/2004	11/4/2014

d. Name of Patent Owner
Euro-Celtique S.A.

Address *(of Patent Owner)*
122 Boulevard de la Petrusse

City/State
L-2330 Luxembourg

ZIP Code	FAX Number *(if available)*
	44-207-408-0714
Telephone Number	**E-Mail Address *(if available)***
44-207-493-3842	

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)

☞ Philip C. Strassburger, Esq.

Address *(of agent or representative named in 1.e.)*
Purdue Pharma L.P.
One Stamford Forum

City/State
Stamford, CT

ZIP Code	FAX Number *(if available)*
06901-3431	(203) 588-6391
Telephone Number	**E-Mail Address *(if available)***
(203) 588-7639	philip.strassburger@pharma.com

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)

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

3. Drug Product (Composition/Formulation)

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 which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

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

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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
Philip C. Strassburger CSPTO Reg No. 34,258	Sept. 13, 2004

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

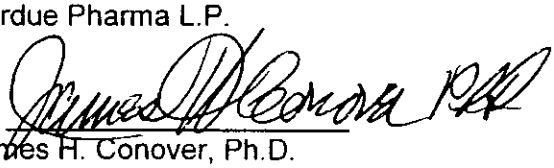
Name Philip C. Strassburger, Esq.	
Address Purdue Pharma L.P. One Stamford Forum	City/State Stamford, CT
ZIP Code 06901-3431	Telephone Number (203) 588-7639
FAX Number *(if available)* (203) 588-6391	E-Mail Address *(if available)* philip.strassburger@pharma.com

ATTACHMENT 3

PARAGRAPH I CERTIFICATION

To the best of our knowledge there are no patents listed in the Orange Book with respect to any drug products which claim or are similar to the drug product for which approval is sought; and we are aware of no unexpired patents, listed or not covering drug products, which are the subject of studies relied upon by Purdue in this application for which a right of reference is required.

Purdue Pharma L.P.

By 
James H. Conover, Ph.D.

Dated: October 8, 1999

PURDUE

Purdue Pharma L.P.
100 Connecticut Avenue
Norwalk, CT 06850-3590
(203) 853 0123
Fax (203) 838 1576

October 11, 1999

Via Facsimile and Federal Express

GENERAL CORRESPONDENCE: RESPONSE TO FDA REQUEST FOR INFORMATION

DESK COPY (COVER LETTER ONLY) TO DEBORAH FONG, PROJECT MANAGER and CORINNE MOODY, CHIEF, PROJECT MANAGEMENT STAFF

Cynthia McCormick, M.D.
Director,
Division of Anesthetic, Critical Care
and Addiction Drug Products
Office of Drug Evaluation 2
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-170, Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

ORIGINAL

NEW CORRESP

Re: **NDA #21-044**
Palladone ™ (hydromorphone hydrochloride)
Controlled-Release Capsules

Dear Dr. McCormick:

Please refer to the Purdue Pharma L.P. ("PPLP") New Drug Application #21-044 for Palladone ™ (hydromorphone hydrochloride) Controlled-Release Capsules submitted to the Agency on December 29, 1998. Please also refer to the Agency's letter dated September 2, 1999. PPLP responds to the Agency's requests made in that letter as follows. [For ease of review, the Agency's requests are quoted in bold and PPLP's responses appear in italicized regular print.]

FDA Request No. 1

A revised Form 356h, specifying that the NDA is being submitted under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (check the box marked 505(b)(2) under section entitled Application Information), in accordance with 21 CFR 314.50 (a)(2).

PPLP Response to Request No. 1

A revised Form 356h specifying that the NDA is being submitted under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act is submitted with this letter as Attachment 1.

FDA Request No. 2

Patents on this drug or use of this drug, in accordance with 21 CFR 314.53.

PPLP Response to Request No. 2

The following patents are submitted with this letter as Attachment 2: Patent Number 5,958,452 and Patent Number 5,478,577.

FDA Request No. 3

Patent certification(s) on any listed drug(s), in accordance with 21 CFR 314.50(i).

PPLP Response to Request No. 3

A Paragraph I Certification is submitted with this letter as Attachment 3.

FDA Request No. 4

Information regarding the period(s) of marketing exclusivity, if any, on any listed drug(s). Please refer to 21 CFR 314.108 for further information.

PPLP Response to Request No. 4

None.

FDA Request No. 5

Duration of marketing exclusivity to which you believe you are entitled, if any, if this NDA is approved. Please refer to 21 CFR 314.50(j) and 21 CFR314.108 for information.

PPLP Response to Request No. 5

We believe that we are entitled to three years of marketing exclusivity if this NDA is approved.

Cynthia McCormick, M.D.
Palladone ~ (hydromorphone hydrochloride) Controlled-Release Capsules
NDA #21-044
October 11, 1999

FDA Request No. 6

List of the sections within your NDA on which you expect this Division to rely during our review, to which you do or do not have right of reference, as defined in 21 CFR 314.3(b).

PPLP Response to Request No. 6

The sections within our NDA on which we expect this Division to rely during its review, to which we do or do not have right of reference, as defined in 21 CFR 314.3(b), are all sections within our NDA. We are not aware of any exclusivity that would affect this review.

We look forward to your continued review of this application.

Sincerely yours,

for James H. Conover, Ph.D.
Executive Director,
U.S. Regulatory Affairs
Telephone: (203) 854-7280
Facsimile: (203) 851-5229

JHC:jmm
Attachments

13. PATENT INFORMATION

The following patent information applies to the 12, 16, 24 and 32 mg Palladone® tablets (NDA # 21-044), the subject of this New Drug Application.

1.	IND Number	#38,424
2.	Applicant:	Purdue Pharma L.P. 100 Connecticut Avenue Norwalk, CT 06850-3590
3.	Listed Drug:	Palladone® (hydromorphone hydrochloride) Capsules
4.	Indication(s):	C
5.	Strengths:	12, 16, 24 and 32 mg
6.	Dosage Form:	Controlled-Release Capsules
7.	Patent Nos.:	4,844,909 4,990,341 5,478,577 5,672,360

13. PATENT INFORMATION

The following patent information applies to the 12, 16, 24, and 32 mg strengths of hydromorphone hydrochloride (controlled-release) capsules which is the subject of this New Drug Application.

1.	Patent Number and Expiration Date	4,844,909; expires October 26, 2007
2.	Type of Patent	Drug Product
3.	Name of Patent Owner	Euroceltique, S.A.
4.	US Agent	Davidson, Davidson & Kappel, LLC 1140 Avenue of the Americas New York, NY 10036

Declaration:

The undersigned declares that Patent No. 4,844,909 covers compositions of **hydromorphone hydrochloride controlled-release capsules**.

Michael Friedman
Vice President
Purdue Pharma L.P.

EXCLUSIVITY SUMMARY FOR NDA # 21-044 SUPPL #_____

Trade Name Palladone (hydromorphone hydrochloride extended release) Capsules

Generic Name hydromorphone hydrochloride

Applicant Name Purdue Pharma HFD# 170

Approval Date If Known PDUFA date September 26, 2004
Division action date September 24, 2004

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_X__/ NO /___/

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

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 /_X__/ NO /___/

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

3 years

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

YES /___/ NO /_X__/

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

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

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

YES /___/ NO /_X__/

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES /_ __/ NO /___/

If "yes," identify the approved drug product(s) containing the

active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

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

YES /___/ NO /___/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

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

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical

investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_x__/ NO /___/

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

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

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

YES /_X__/ NO /___/

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

_____

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

YES /___/ NO /_X _/

(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 /_X__/
(Not the extended release form)

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:

HD95-0801and HD95-0802 were two period crossover trials of identical design comparing extended-release to immediate release hydromorphone hydrochloride in subjects with cancer-related or chronic nonmalignant pain.

Study HMP-3006 was a multiple-dose, double-blind, randomized, parallel-group, multicenter, placebo-controlled study assessing the efficacy and safety of HHER dosed once daily in moderate to sever chronic non-malignant pain.

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

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

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency

to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

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

_____ _____

_____ _____

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

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

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

_____ _____

_____ _____

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

HD95-0801and HD95-0802 were two period crossover trials of identical design comparing extended-release to immediate release hydromorphone hydrochloride in subjects with cancer-related or chronic nonmalignant pain.

Study HMP-3006 was a multiple-dose, double-blind, randomized, parallel-group, multicenter, placebo-controlled study assessing the efficacy and safety of HHER dosed once daily in moderate to sever chronic non-malignant pain.

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?

Investigations listed above-

IND # 38,424 YES /_X__/ ! 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 /__X_/

If yes, explain: _____

Signature: Sara E. Stradley, MSc --Sept 20, 2004
Title: Regulatory Project Manager

Concurred by Parinda Jani-- Sept 20, 2004
Title: CPMS,

Signature: Bob Rappaport, MD
Title: Division Director

Form OGD-011347 Revised 05/10/2004

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

/s/

Robert Meyer
9/23/04 12:39:36 PM
For Dr. Rappaport

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-044 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: July 26, 2004 (5th review cycle) **Action Date:** September 26, 2004
Original application date December 28, 1998

HFD -170 **Trade and generic names/dosage form:** Palladone (hydromorphone hydrochloride extended-release) Capsules 12-, 16-, 24-, and 32- mg

Applicant: Purdue Pharma **Therapeutic Class:** 3S

Indication(s) previously approved: none

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

Number of indications for this application(s): one

Indication #1: Provides for the use of Palladone (hydromorphone hydrochloride extended-release) Capsules 12-, 16-, 24-, and 32-mg for the management of persistent, moderate to severe pain in opiate-tolerant patients requiring continuous, around-the-clock analgesia with a high potency opioid for an extended period of time, generally weeks to months or longer.

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

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

X **No: Please check all that apply:** ___Partial Waiver __X__Deferred ___Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

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.** 0	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** 16	**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**
- X **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): September 24, 2009

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}

Regulatory Project Manager

Concurred by Parinda Jani, CPMS, Sept 20, 2004

cc: **NDA 21-044**
HFD-960/ Grace Carmouze

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

(revised 12-22-03)

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

/s/

Sara Stradley
9/23/04 10:37:27 AM

16. DEBARMENT CERTIFICATION

Purdue Pharma L.P. 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.

Richard J. Fanelli. Ph.D.
Director, U.S. Regulatory Affairs

1/11/02
Date

L:\JMM\Palladone - HHER\HMP-3006 submission in 2002\Section 16 - Debarment Certification.doc

16. DEBARMENT CERTIFICATION

Purdue Pharma L.P. 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.

James H. Conover, Ph.D.
Executive Director, Regulatory Affairs

10-28-98
Date

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)443-3741

MEMORANDUM

DATE: October 4, 2001

TO: File, NDA 21-044

FROM: Bob A. Rappaport, M.D.
Deputy Director, DACCADP
Team Leader, Anesthetic Drug Group

RE: Addendum to Clinical Review of Response to Approvable Letter

Financial Disclosure: The sponsor has documented that none of the investigators had reportable financial interests.

Cc: Original NDA 21-044
HFD-170: Division File
HFD-170:
McCormick
Rappaport
Milstein

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

/s/

Bob Rappaport
10/4/01 05:56:14 PM
MEDICAL OFFICER

Purdue Pharma L.P.
Regulatory Affairs
One Stamford Forum, Stamford, Connecticut06901-3431, USA
Tel: +1 (203) 588-8365 • Fax: +1 (203) 588-6229

Facsimile

To: Judit Milstein

From: Dr. Richard J. Fanelli
Director, U.S. Regulatory Affairs

Re: Palladone Financial Disclosure
NDA # 21-044

Date: October 4, 2001

FAX: (301) 443-7068

Total Number of Pages (Including this page): 1

If Transmission Is Not Complete, Please Call Telephone: (203) 588-8365

☐ Urgent ☒ For Review ☐ Please Comment ☐ Please Reply

Dear Ms.Milstein,

As you just requested, in Section 19 of our complete response dated March 30, 2001, the investigators listed are all those involved in the conduct of Study HMP 3005.

There were no other investigators involved in the conduct of this study.

If there are any questions, please feel free to contact me at (203) 588-8365.

Regards,

Dr. Richard J. Fanelli
Director, U.S. Regulatory Affairs

Phone: (203) 588-8365
Fax: (203) 588-6229

4 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

9/23/04

Office Director's Sign-Off Memorandum

Date:	Thursday, September 23, 2004
NDA:	21-044
Sponsor:	Purdue Pharma, L.P.
Proprietary Name:	Palladone (hydromorphone HCl extended-release capsules), 12 mg, 16 mg, 24 mg and 32 mg
NDA Code:	Type 3S NDA

NOTE: As a 3S NDA, this action would ordinarily be taken appropriately at the Division level (though there has been considerable Office and even Center-level input into the deliberations). In fact, all past actions on this application have been signed at the division level. However, as Dr. Rappaport is unavailable at the time of the due date for this resubmission, I am signing the package in his stead and therefore doing the final memo.

Background: This NDA was originally submitted by Purdue Pharma on December 29, 1998. The NDA is for an extended-release, high drug content formulation of hydromorphone, the active ingredient in such immediate release products as Dilaudid. Several actions have been taken over the years, with the early deficiencies in the first cycles being the inadequacy of the clinical data supporting the application. Upon review of the initial application, the Division determined that the clinical studies did not provide adequate evidence of efficacy. A complete response to the third action letter was received in March 2002. That 2002 submission did include data providing sufficient evidence of Palladone being safe and effective for its proposed use. However, inspection of the manufacturing site for the drug product was found to have significant GMP deficiencies, which led to a Withhold Approval recommendation on the EERs. Therefore a further action other than an approval was taken in September 2002 (in this case, an "approvable"). This approvable letter noted the following:

> *"While not specifically a condition of approval, agreement on the elements of the Risk Management Program designed at minimizing the risk of abuse and diversion of this product should be resolved before this product is marketed."*

Prior to receipt of the resubmission following the 2002 action, the FDA convened a meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) in September 2003, to discuss risk management issues with high potency opiate analgesics in general and the proposed RMP for Palladone in specific. Purdue Pharma presented their RMP for Palladone and OxyContin at this meeting. The ALSDAC advised FDA that an RMP was essential to the marketing of Palladone, to assure that it would not be misused, abused or diverted. At this meeting, Purdue Pharma stated that they planned to do a limited rollout plan for promotion, targeting knowledgeable pain physicians (e.g., oncologists) that could be assessed at various points before moving from one phase of the plan to the next. The company originally planned to do the limited marketing rollout in only 6 month stages. While the committee recommended to us that this kind of targeted, limited rollout was advisable, they recommended a longer duration prior to broadening the marketing, to allow for adequate assessment of the results of the provider education and marketing in assuring proper medical use.

On December 17, 2003, the Division and representatives from the Office of New Drugs, the Office of Drug Safety, the Controlled Substances Staff, and the Office of the Center Director met with Purdue to discuss the outcomes of the ALSDAC meeting and the company's plans for further development of the Palladone RMP. In this meeting, the FDA provided clear expectations for what we would consider to be a thorough and complete RMP, particularly regarding the implementation of a limited rollout for the promotion and marketing of Palladone.

A complete response to the September 2002, letter was received on May 17, 2004. This submission consists of evidence documenting that the GMP deficiencies at the drug product manufacturing site have been satisfactorily addressed, and includee a proposed final RMP and proposed final product labeling. It also included genotoxicity data on one of the impurities (morphinone besylate). These studies found that the substance was in fact clastogenic in CHO cells. After extensive review of the proposed RMP contained in that resubmission, including consultative reviews by the Controlled Substances Staff and the Office of Drug Safety, the division/ODE determined that the RMP would require some substantive changes and additions will be necessary before we are able to conclude that the plan is adequate to assure the safe marketing of Palladone. These changes and additions were summarized in Dr. Rappaport's action memo and included:

- The submission of all data regarding abuse, misuse, overdose, addiction or diversion associated with hydromorphone, from RADARS and other surveillance programs, and appropriate analyses of that data.
- The submission of a plan for submitting reports of abuse, misuse, overdose, diversion and deaths associated with Palladone or other hydromorphone containing products
- The submission of a plan that describes how interventions will be reported to the Agency.
- The submission of a detailed plan for educating prescribers regarding the potential for addiction in patients treated with Palladone
- The submission of a Medication Guide
- The submission of a plan to address hydromorphone-associated abuse, misuse, and addiction in geographical regions already showing a signal of one or the other of these concerns
- The submission of a specific timeline that addresses all features of the limited rollout, to include adequate opportunity for Agency review and feedback.

Additionally, there were labeling changes needed (including converting the patient package insert to a MedGuide), and this need for further labeling changes was the basis for the approvable action in July 16th, 2004.

Current Submission: The sponsor quickly resubmitted in response to the last action, with the resubmission dated July 23rd and received on July 26th. This scope of data in the resubmission meant that this review was subject to a 2-month deadline, with a due date of September 26th, 2004. Since this is a Sunday, our plan is to take action on the 24th. The sponsor submitted revised labeling (including a MedGuide) and revisions to the RMP intended to address the above points listed in the previous action letter. For the most part,

they did do so. However, a meeting was held between the FDA (DACCADP, ODE II, CSS and ODS/OPaSS) and Purdue on August 30th, 2004, to reach a common understanding of what else was needed in terms of optimizing the RMP and labeling and, particularly, agreeing on the reporting of data to FDA resulting from the RMP actions.

Besides the MedGuide issue, the main labeling problem that proved to be of some difficulty in solving with the company was a statement carried over from the approved OxyContin label that the occurrence of addiction with medical use for this product was — ' FDA does not believe there are data to support that assertion, even in patients who have no history of prior drug abuse, as — neans a rate lower than 1/1000 or even 1/10,000 depending on your definition. We have arrived at satisfactory labeling in this regard and it was my stated expectation that Purdue would also amend their OxyContin labeling to remove this reference to this — of addiction.

As for the RMP elements itself, the basic elements are meant to address appropriate medical use (especially assuring that patients who receive it are opiate-tolerant), misuse/abuse and diversion, and protection of children. The latter is through proper child-resistant packaging and associated labeling. The former issues are addressed by many elements, including labeling, education (provider and patient), surveillance for misuse, abuse, addiction and diversion, limited launch program (with voluntary presubmission of marketing pieces post-launch), and supply chain integrity assurance.

With amendments to the proposal received after our August 30th meeting (notably a September 10th, 2004 submission), the RMP is now deemed to be adequate to allow for approval. Purdue has committed to an extensive RMP that includes providing FDA with monthly reports of non-expedited MedWatch reports for overdoses and deaths (occurring within the confines of labeling), reports of abuse, misuse, or addiction associated with Palladone, AEs in anyone under age 18, AEs in opiate-naïve patients, medication errors with this product and other information, such as any reports of loss of product at the pharmacy level. Purdue has also committed to supplying quarterly reports that include not only the required PSUR, but also includes reports on the RADARS system data, reports of any interventions taken by Purdue to address issues of misuse, abuse and diversion, External Advisory Board minutes, field SOP findings and other information. Finally, at twice-yearly intervals, Purdue has committed to providing reports that will address serious AEs, including overdose and deaths. Finally, within 15 months of distribution of Palladone, the company will submit a report on the limited marketing or rollout results, focusing on the appropriateness of the patients prescribed Palladone (e.g., were they opiate tolerant).

At this point, FDA is deferring pediatric studies under PREA to 5 years beyond the action date. We did not feel there was justification to insist this work be done pre-approval, as there are many alternatives available at present for the pediatric population. FDA is also citing in its letter an agreement byr Purdue to lower the levels of their clastogenic impurity, the morphinone besylate post approval to levels of — ppm.

Director's Recommendation/Action: Approval, with the agreed upon RMP as submitted in final on September 21, 2004 and agreed upon labeling.

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/s/

Robert Meyer
9/23/04 04:58:57 PM
MEDICAL OFFICER

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

TO: Richard Fanelly (Purdue Pharma)
Phone Number: (203) 588-8365
Fax Number: (203) 588-6229

FROM: Judit Milstein, Regulatory Project Manager

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCTS

CDER/DAACADP (HFD-170), 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-7440 FAX: (301) 443-7068

Total number of pages, including cover sheet 6 : Date: 4-Oct-01

COMMENTS: Find enclosed the copy of the action letter for NDA 21-044

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 17, 2004

To: Bob A. Rappaport, M.D., Director
Division of Anesthetic, Critical Care
and Addiction Drug Products (HFD-170)

Through: Deborah B. Leiderman, M.D., Director
Controlled Substance Staff (HFD-009)

From: Silvia N. Calderon, Ph.D., Team Leader
Controlled Substance Staff (HFD-009)

Subject: Consultation regarding proposed Risk Management Program
NDA 21-044, Palladone Extended Release Capsules
Sponsor: Purdue Pharma L.P.
Submission reviewed in this consult: Response to FDA request for information submitted September 10 and September 14, 2004

BACKGROUND

This memorandum responds to the Division of Anesthetic, Critical Care, and Addiction Drug Products's request for CSS consultation on the Palladone submissions dated September 10 and September 14, 2004.

The submission dated September 10, 2004 answers primarily the Agency's request on the reporting timelines and types of reports. The Sponsor committed to send monthly reports that will include:

a- Labeled overdose and deaths associated with Palladone capsules
b- Reports of abuse, addiction and misuse associated with Palladone. The Sponsor has defined the term misuse as, "the use of a medication other than as intended, whether willful or unintentional." Therefore, this definition allows for the inclusion of reports related to improper patient selection, use of the product in acute pain, and the use of the product in patients who are not opioid tolerant.
c- Adverse events associated with reports of exposure to Palladone involving children 18 years of age or younger
d- Adverse events occurring in "opioid-naïve" persons who use Palladone
e- Medication errors associated with the administration of Palladone
f- Reports of documented safety concerns identified via surveillance

In addition the Sponsor committed to submit quarterly RADARS reports that will not include full analysis of the information gathered through this active surveillance system. Full reports will be sent biannually.

The September 14, 2004 submission proposes language to replace the following statement, [ ] mentioned under the WARNINGS section, "Misuse, Abuse and Diversion of Opioids" subsection of the proposed label, by [ ]

RECOMMENDATIONS

1. CSS finds the Sponsors' reporting proposal satisfactory.
2. CSS does not agree with the label language proposed by the Sponsor. CSS objects to the use of the word — " to describe the incidence of abuse and addiction in the setting of opioid analgesic treatment. Data are not available to establish the true incidence of addiction in chronic pain patients. The Sponsor included a document recently published by the Drug Enforcement Administration and health care professionals. CSS finds the information submitted not supportive for the inclusion of the term — The term — ' indicates a 1/10,000 frequency of adverse event ocurrence, and certainly several recent publications (Brands *et al.*, 2004; Fishbain *et al.*, 1992; Manchikanti *et al.*, 2003; Saper *et al.*, 2004) indicate the contrary. The true incidence of addiction in the chronic pain treated population is unknown, but it has been reported to be as low as 3% and as high as 24 %.

REFERENCES

1. Brands, B., Blake, J., Sproule, B., Gourlay, D., Busto, U. Prescription Opioid Abuse in Patients Presenting for Methadone Maintenance Treatment. Drug and Alcohol Dependence 2004, 73, 199-207.
2. Fishbain, D.A., Rosomoff, H.L., Rosomoff, R.S. Drug Abuse, Dependence, and Addiction in Chronic Pain Patients. Clin. J. Pain, 1992, 7, 77-85
3. Manchikanti, L., Pampati, V., Damron, R. N., Beyer C. D., Barnhill, R.C., Fellows, B. Prevalence of Prescription Drug Abuse and Dependency in Patients with Chronic Pain in Western Kentucky. J Ky Med Assoc. 2003, 101, 511-517.
4. Saper, J. R., Lake III, A. E., Hamel, R.L., Lutz, T.E., Branca, B., Sims, D.B., Kroll, M.M. Daily Scheduled Opioids for Intractable Head Pain. Long Term Observations of a Treatment Program. Neurology, 2004, 62, 1687-1694.

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/s/

Silvia Calderon
9/17/04 12:51:19 PM
CHEMIST

Deborah Leiderman
9/17/04 01:39:21 PM
MEDICAL OFFICER

Stradley, Sara

From: Stradley, Sara
Sent: Monday, September 20, 2004 3:26 PM
To: 'Fanelli, Richard'
Cc: Stradley, Sara
Subject: RE: Palladone NDA #21-044: PI Removal of ' —
Sensitivity: Confidential

Rich
We have the following change to make in the WARNINGS section of the label. This new phrase will be something we plan to add to all high concentration opioid products.

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opiate analgesic products carry the risk of addiction even under appropriate medical use.

The removal of the word [ ] from the sections of the label listed below is acceptable.

Sara

-----Original Message-----
From: Fanelli, Richard [mailto:Richard.Fanelli@pharma.com]
Sent: Monday, September 20, 2004 1:00 PM
To: Sara E. Stradley (E-mail)
Subject: Palladone NDA #21-044: PI Removal of ' —
Importance: High
Sensitivity: Confidential

Sara -
As we discussed this morning, and as discussed during our teleconference on Friday September 17th, we agreed to remove the word [ ] " from the 6 (six) locations listed below, as found in our pdf version of the Palladone label submitted on September 17th.

If you need this information submitted in another manner, or have any other questions, please let me know.

Rich

1. final paragraph of boxed warning
2. line 239
3. line 255
4. line 748
5. line 1029
6. line 1127

Richard J. Fanelli, Ph.D.
Senior Director, US Regulatory Affairs
Purdue Pharma L.P.

Tel: (203) 588-8365
email: richard.fanelli@pharma.com

Appears This Way
On Original

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/s/

Sara Stradley
9/20/04 03:29:22 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-044

INFORMATION REQUEST LETTER

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

9/17/04

Attention: Richard J. Fanelli, Ph.D.
Senior Director

Dear Dr. Fanelli:

Please refer to your December 28, 1998 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Palladone (hydromorphone hydrochloride extended-release) Capsules.

We also refer to your submission dated September 10, 2004 and the meeting held between representatives of your company and the Agency on August 30, 2004 to discuss the issues identified in the July 16, 2004 action letter.

We have the following additional comments from the Office of Drug Safety concerning the frequency of reporting and the contents of the surveillance activities reports.

Monthly Reports

1. The monthly reports should be clearly sorted and labeled into appropriate categories. FDA would like to discuss with you the method and manner used to sort and separate the reports into appropriate categories. FDA suggests meeting with the you either near approval or after submission of the first monthly report to discuss format modifications or improvements regarding the monthly reports.

2. Adverse events identified as items a, b, c, d, and e that will be submitted in the monthly report should also be submitted in the subsequent periodic report as normally required by the regulations 21 CFR 314.80. This will ensure that the adverse events (AEs) are entered into the AERS database.

3. The reports of documented safety concerns (item f.) identified via surveillance do not need to be submitted on MedWatch forms for documentation, but should be submitted and clearly labeled in a format to allow review and analysis by FDA.

4. Please send the four (4) desk copies of the monthly report, quarterly report, and six month report to the attention of ODS-IO Project Manager, HFD-400.

Quarterly Reports

1. When submitting the "Minimum Candidate Rollout Metrics-2" information using RADARS® System to monitor for signals of abuse and diversion, please include the outpatient drug use patterns in the following manner:

   a. Use sales and prescription data to monitor for disproportionate increases by geographic area.

   b. Look for inappropriate prescribing by using patient-level, Rx drug use longitudinal data to look for evidence of patients switching between insurance and cash payments and/or doctor/pharmacy shopping by geographic area.

2. The quarterly reports should also include:

   a. Interventions undertaken and known consequences/impacts

   b. External Advisory Board (EAB) meeting minutes

   c. Field force SOP findings

PPLP Report of Limited Rollout Metrics

1. The Prior Therapy Report should be clearly labeled and should be submitted not 15 months after dispensing of Palladone™ begins, but as part of the Six-Month Reports.

2. The Prescription by Specialty Report should be clearly labeled and submitted as part of the Quarterly Reports.

If you have any questions, call Sara E. Stradley, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Supervisory CSO
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
9/17/04 11:34:15 AM

MEMORANDUM OF TELECON

DATE: September 17, 2004

APPLICATION NUMBER: NDA 21-044, Palladone (hydromorphine HCl extended-release capsules)

BETWEEN:

Name: Richard J. Fanelli, PhD, Senior Director, US Regulatory Affairs
J. David Haddox, DDS, MD, Vice President, Risk Management & Health Policy
Ellen Ingber, Executive Director, Project Management
Anthony Santopolo, MD, Vice President, US Regulatory Affairs

Phone: 301-827-7413
Representing: Purdue Pharma

AND

Name: Bob Meyer, MD, Director, ODEII
Rigoberto Roca, MD, Deputy Director, DACCADP
Silvia Calderon, PhD, Interdisciplinary Scientist, CSS
Sara E. Stradley, Regulatory Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products

SUBJECT: Palladone Package Insert

The Sponsor was told that the following underlined sentence (submitted on September 17, 2004) located in the WARNINGS section of the label would need to be revised once again. The Division stated that the data provided by the Sponsor still did not support the use of the term " —

( )

The Sponsor was concerned that removal of this statement would eliminate consistency with a nearly identical statement in the Oxycontin package insert. The Division advised the Sponsor that this section of the label (i.e, the use of the term — should also be revised in the Oxycontin package insert.

On September 20, 2004, the Sponsor agreed to the following revision in the Palladone package insert.

> Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carry the risk of addiction even under appropriate medical use.

In a separate conversation with the Sponsor, the Division requested that "carry" be changed to "carries" in the above statement and the Sponsor concurred with this grammatical change.

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/s/

Sara Stradley
9/23/04 01:02:08 PM
CSO

3 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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

DATE: September 16, 2004

TO: Bob A. Rappaport, M.D., Director
Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170

FROM: Anne Trontell, M.D., M.P.H., Deputy Director
Office of Drug Safety
(ODS), HFD-400

DRUG: Palladone™ (Hydromorphone HCl Extended-Release Capsules)

NDA #: 21-044

SPONSOR: Purdue Pharma, L.P.

SUBJECT: ODS review of General Correspondence: Response to FDA Request for Information submitted September 10, 2004

PID #: D040603

The Office of Drug Safety (ODS) reviewed the general correspondence submitted in response to the FDA request for information submitted on September 10, 2004 and has the following comments in reference the attached document, Palladone™ Capsules-Reports of Surveillance Activities.

Monthly Reports

- The monthly reports should be clearly sorted and labeled into appropriate categories. FDA would like to discuss with the sponsor the method and manner used to sort and separate the reports into appropriate categories. FDA suggests meeting with the sponsor either near approval or after submission of the first monthly report to discuss format modifications or improvements regarding the monthly reports.

- Adverse events identified as items a, b, c, d, and e that will be submitted in the monthly report should also be submitted in the subsequent periodic report as normally required by the regulations 21 CFR 314.80. This will ensure that the AEs are entered into the AERS database.

- The reports of documented safety concerns (item f.) identified via surveillance do not need to be submitted on MedWatch forms for documentation, but should be submitted and clearly labeled in a format to allow review and analysis by FDA.

- Please send the four (4) desk copies of the monthly report, quarterly report, and six-month report to the attention of ODS-IO Project Manager, HFD-400.

Quarterly Reports

- When submitting the "Minimum Candidate Rollout Metrics-2" information using RADARS® System to monitor for signals of abuse and diversion, please include the outpatient drug use patterns in the following manner:
    - use sales and prescription data to monitor for disproportionate increases by geographic area
    - look for inappropriate prescribing by using patient-level, Rx drug use longitudinal data to look for evidence of patients switching between insurance and cash payments and/or doctor/pharmacy shopping by geographic area.

- The quarterly reports should also include:
    - Interventions undertaken and known consequences/impacts
    - EAB meeting minutes
    - Field force SOP findings

PPLP Report of Limited Rollout Metrics

- The Prior Therapy Report should be clearly labeled and should be submitted not 15 months after dispensing of Palladone™ begins, but as part of the Six-Month Reports.
- The Prescription by Specialty Report should be clearly labeled and submitted as part of the Quarterly Reports.

ODS Team:
Mary Dempsey, Project Management Officer, ODS-IO
Claudia B. Karwoski, Pharm.D, Scientific Coordinator, ODS-IO
Mary Willy, Ph.D., M.P.H., Epidemiology Team Leader, DDRE

Anne Trontell, M.D., M.P.H.
Deputy Director
Office of Drug Safety
(ODS), HFD-400

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/s/

Mary Dempsey
9/16/04 03:08:38 PM
DRUG SAFETY OFFICE REVIEWER

Anne Trontell
9/16/04 04:41:49 PM
DRUG SAFETY OFFICE REVIEWER
For the Office of Drug Safety and with agreement
of Paul Seligman

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-044

9/10/04

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Richard J. Fanelli, Ph.D.
Director, US Regulatory Affairs

Dear Dr. Fanelli:

Please refer to the meeting between representatives of your firm and FDA on August 30, 2004. The purpose of the meeting was to discuss the action letter dated July 16, 2004 and the risk management plan for Palladone (hydromorphone hydrochloride extended-release) Capsules.

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, call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

INDUSTRY MEETING MINUTES

Meeting Date: August 30, 2004

Location: Parklawn Building, Conference Room B

NDA/ Name: NDA 21-044

Sponsor: Purdue Pharma

Drug: Palladone (hydromorphone hydrochloride extended-release) Capsules

Type of Meeting: Requested by the Agency

Meeting Chair: Bob Rappaport, MD, Division Director
Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170

Purdue Pharma	Title
Richard J. Fanelli, PhD	Senior Director, US Regulatory Affairs
J. David Haddox, DDS, MD,	Vice President, Risk Management & Health Policy
Ellen Ingber	Executive Director, Project Management
Michael Innaurato	Group Executive Director, Marketing
Robert Reder, MD	Vice President, Medical Affairs & Worldwide Drug Safety
Anthony Santopolo, MD,	Vice President, US Regulatory Affairs
Sidney Schnoll, MD, PhD	Executive Medical Director, Health Policy
Janine Spaulding	Product Manager, Marketing
FDA	**Title**
Bob Meyer, MD	Director, OND II
Bob A. Rappaport, MD	Division Director, DACCADP
Paul Seligman, MD	Office Director, OPSS
Anne Trontell, MD	Deputy Office Director, OPSS/ODS
Brenda Marques, PharmD	Senior Regulatory Rev. Officer, DDMAC
Sara Stradley, MS	Regulatory Project Manager, DACCADP
Deborah Leiderman, MD	Director, CSS
Silvia Calderon, PhD	Pharmacologist, CSS

Meeting Objective(s): The purpose of this meeting was to discuss the July 16, 2004 action letter and the risk management plan.

General Discussion: After introductions, the meeting focused on the risk management plan for Palladone. The slides presented are in italics. The issues listed are from the July 16, 2004 action letter and Purdue's responses to these items received July 26, 2004. Any discussion follows.

PACKAGE INSERT

The product labeling must be revised and finalized.

1. *We have reviewed and revised your proposed labeling. The revised labeling is enclosed. Prior to approval, you must submit revised draft labeling for the drug that is identical in content to the enclosed labeling. If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.*

   PPLP Response:
   See attachments 2-4 for revised draft labeling for this product as requested. The PI is provided as a red-line strikeout version (Attachment 2) using the document you sent to us on July 16, 2004, as well as an annotated red-line strikeout version (attachment 3), and a clean version (attachment 4).

   Discussion
   The Agency stated that the package insert will be discussed in detail at a later time in the review clock. However, the Agency did want to state that the sentence in the WARNINGS section [redacted] would not be allowed in the label. The Agency suggested that the Sponsor send in alternative language for the Division to review. The Sponsor stated that they believed that the statement was correct and expressed concern that a change now would be a liability to them. The Agency requested that the Sponsor provide data to support the term [redacted] and the Sponsor agreed to provide this information. The Agency agreed to provide the Sponsor with reference citations regarding the wide range of addiction rates in chronic pain patients (see list of references at end of document).

   The Sponsor clarified that the rate of addiction is rare in patients without a history of substance abuse, however, the Agency stated that Palladone is for opioid tolerant patients. The Agency requested that the Sponsor formally propose a labeling change based on this distinction and the Sponsor agreed to this proposal.

2. *Pursuant to 21 CFR Part 208, FDA has determined that Palladone poses a serious and significant public health concern requiring distribution of a Medication Guide. Palladone is a drug product for which patient labeling could help prevent serious adverse effects. Palladone has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or to continue to use, the product. Palladone is important to health, and patient adherence to directions for use is crucial to the drug's effectiveness. The Medication Guide for NDA 21-044 Palladone should address concerns about overdose, addiction, and proper use. In accordance with 21 CFR 208.24, you will be responsible for ensuring the following:*

   a. *That a Medication Guide for Palladone is available for every patient who is dispensed a prescription for Palladone.*

   PPLP response:
   See attachments 2-4 for a draft Medication Guide for Palladone. In order to make this medication Guide available for everyone patient dispensed a prescription for Palladone, we propose to provide this Medication Guide using some or all of the following methods:

   - *To make med guide available in appropriate format to vendors who provide electronic information about drugs to retail pharmacies for the purposes of accompanying information in the prescription dispensing process.*
   - *To make a copy of the med guide available on our website in an easily downloadable format.*
   - *To provide adequate numbers of hard copies (e.g. tear pads) in every wholesale order that is shipped. Wholesalers, in turn, can forward these tear pads with each retail order.*
   - *To provide tear pads of the med guide to any HCP upon request.*

   b. *That the label of each container of Palladone includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom Palladone is dispensed.*

   PPLP response:
   See attachment 5 for revised container labels that contain the requested instruction.

   c. *That the label of each container includes a statement about how the Medication Guide is provided.*

   PPLP response:
   See attachment 5 for revised container labels that indicate that meds guides accompany the product container.

Discussion
The Sponsor stated that they submitted the Medication Guide with the resubmission dated July 23, 2004 (received on July 26, 2004) and the Agency stated that it is currently under review in the Office of Drug Safety.

RISK MANAGEMENT PLAN

1. *Establishing a baseline for current hydromorphone exposure, using information collected as part of Purdue's current active surveillance systems. This baseline information and any subsequent changes will allow for the assessment of the utility and value of your proposed surveillance tools as part of the Palladone RMP.*

   PPLP Response:
   Reference is made to the RADARS System Supplemental Report Focused on Hydromorphone that was submitted in correspondence dated July 13, 2004. This report contains the baseline information that is available through Purdue's current active surveillance systems.

   Discussion
   The Agency stated that the hydromorphone data is currently under review. The Agency will contact the Sponsor to establish a mutually agreed upon format that is efficient and informative for nonstandard reports requested by the Agency.

2. *Timely analysis of safety issues, including overdose and deaths, related to Palladone and how FDA may be notified of these issues. For instance, it would be useful to include the following postmarketing adverse event reports as 15-day "Alert Reports," in addition to those required to be reported under 21 CFR 314.80(c)(1)(i):*
   a. *All overdoses and deaths associated with Palladone*
   b. *All reports of abuse, addiction, and misuse associated with Palladone*
   c. *All adverse events and reports of exposure to Palladone involving children 18 years of age or younger*
   d. *All adverse events occurring in "opioid-naïve" persons who use Palladone*
   e. *All medication errors associated with the administration of Palladone*

   PPLP Response:
   We agree that timely analysis of safety issues is important with any new product's market introduction. In response to the categories of particular interest cited above, we proposed submitting the information requested in items a through e in the Quarterly Periodic Reports that are required to be submitted to the FDA for the first three years following approval of Palladone. All postmarketing adverse events that have been received within the reporting period will be included in this report. In these Quarterly Periodic reports, we will provide specific listings of adverse events that fall within these five areas identified by FDA as being of particular interest.

Discussion

The Agency stated that frequent early reports were essential to capture information. The Agency stated that the five items listed were very important regarding public health during a product launch and stated that these five items should be included in 15-day alert reports. The Sponsor replied that they needed a better definition of what the Agency considered "misuse" so that their colleagues could be properly trained to identify "misuse." The Agency stated that this term reflected incorrect use of the product by the patient or by the prescribing physician and clarified that "misuse" should not include patients that took 2 tablets versus the recommended dose of 1 tablet as this is not deliberate misuse and is more an error in dosing. The Agency stated that the Sponsor should be looking at deliberate misuse.

The Sponsor referred to their July 13, 2004 submission where they defined misuse as "the use of a medication other than as intended, whether willful or unintentional." The Agency stated that the Sponsor should be analyzing a subset of this population and requested that they submit a specific definition for this subset population and the Sponsor agreed. The Agency stated that they are not looking for all off-label reports but the Sponsor should focus on problematic use of the drug product. The Sponsor should define what subset of misuse they can capture, especially those not associated with an adverse event.

The Sponsor stated that they have several systems in place to capture potential problems. Their adverse event system captures all of the adverse events. Medication errors may be reported to a salesperson or reported to the medical information hotline. Neither one of these is a validated database. The Sponsor stated that trying to put all of these under one database will cause problems with the collection of data. The Sponsor reiterated that no formal report is collected if no adverse event is associated with the report. The Sponsor clarified that items that are reported but not associated with adverse events are reviewed internally. The Sponsor suggested quarterly reports instead of 15-day reports for the first three years after launch.

The Agency stated that it is important to view the data more frequently than quarterly in order to quickly pick up a signal if there is a problem. The Agency stated that information flow was very important. The Sponsor suggested that monthly reports containing line listings or MedWatch forms could be run and sent to the Agency for review but the report would not contain any analysis. The Agency agreed this might be a good alternative and told the Sponsor that they would be informed after additional internal discussions within the Agency. The Sponsor clarified that the line listings will have all the information, similar to what is contained in a MedWatch report.

The Agency agreed that the term "all" in the five listed items may cause problems for the Sponsor and advised the Sponsor to capture the information to the best of their ability. The Sponsor agreed to explore and propose mechanisms and timing for capturing and reporting to FDA items a through e that are not associated with adverse events, for instance medication errors and reports of pediatric exposures.

3. *Timely submission of RADARS reports as well as reports from other surveillance mechanisms (e.g., DAWN, NSDUH, pertinent product inquiries, and media/medical literature surveillance) to FDA on a regular and frequent basis would facilitate evaluation of your RMP.*

PPLP response:
As indicated previously, please refer to the RADARS System Supplemental Report Focused on Hydromorphone submitted in correspondence dated July 13, 2004. We will provide FDA with similar reports on Palladone and other hydromorphone products at 6 month intervals during the period of the phased launch and annually thereafter. Information from DAWN, NSDUH, pertinent product inquiries, and media/medical literature surveillance will be included in these reports as new data become available. Time is specifically set aside at each of the quarterly meetings of the EAB during which newer data are presented to representatives of Federal Agencies, including FDA.

Discussion
The Agency stated that they wanted quarterly reports during rollout. The Sponsor stated that the first quarter of the rollout will not have much data because of the lag time of sending out questionnaires and the collection of data. Information will be sent to the Sponsor on a quarterly basis and the information would be more meaningful at 6 months. The Sponsor stated that if any serious problem was noted than the Agency would be notified prior to the 6 month date. The Sponsor agreed that a first report at 6 month post rollout and then every quarter is a possibility.

The Agency questioned the information presented at the External Advisory Board (EAB). The Sponsor stated that at the EAB meeting the physicians present the data to the Sponsor and guide them on how to interpret the information. The Agency questioned if this data could be submitted to the Agency. The Sponsor stated that this could be a possible approach but that the data would not be analyzed. The Sponsor will propose a plan to address sending the EAB information to the Agency as part of quarterly reports submitted to the Agency.

The Sponsor will propose data that will be sent to FDA without analysis on a quarterly basis, but with analysis every other quarter (6 months.) Candidate data discussed at the meeting included the following:

- EAB meeting minutes and data presented

- Data generated by the field forces in response to company SOPs and reporting to PPLC General Counsel suspicious reports, in tabular format
- Supply chain loss report
- Rx Patrol
- Media surveillance
- RADARS quarterly data, to include line items (without analysis every other quarter)
- Interventions undertaken and known consequences/impacts reported on a qualitative basis.

4. *Modification of your RMP to provide for the submission, within 15 calendar days of identification, of all reports documenting safety concerns by geographical area that are identified via any surveillance methodologies.*

   PPLP response:
   How we will usefully report specific safety concerns by geographical area will require additional discussion.

   Discussion
   The Sponsor stated that, if geographical information is available, it will be submitted to the Agency. The timing of this type of report will be discussed internally by the Agency and made consistent with the Agency's request for reporting of items in item 2, that is, either monthly or within 15 days. The Agency reiterated that it is important for the Sponsor to keep the Agency in the loop regarding safety issues with Palladone.

5. *Timely reporting to FDA of any interventions you initiate in response to the adverse event information you receive related to Palladone, and how you plan to (1) assess the results of these interventions and (2) apprise FDA of the results.*

   PPLP response:
   In the RADARS System Report Focused on Hydromorphone, provided at 6 month intervals during the period of the phased launch and annually thereafter, we will provide a listing of interventions initiated in response to hydromorphone signals, as described in the updated RADARS System Report submitted to our OxyContin Controlled Release Tablets NDA 20-553 on June 18, 2004 along with our plans to assess the results of these interventions and apprise FDA of the results.

   Discussion
   The Agency requested that the Sponsor keep the Agency informed of any interventions, no matter how minor.

   The Sponsor stated that it is hard to capture intervention in line listings. As more data are captured, the Sponsor will develop intervention programs, if needed. The

Sponsor stated that they can develop intervention programs but they cannot make drug abuse go away. The Agency requested that when the Sponsor initiates an early intervention program, that the Agency should be notified on at least a quarterly basis (see previous item 3, last bullet.) The Sponsor will propose how frequently a report can be submitted to the Agency.

6. *Notification to FDA of instances where you have officially communicated with other Federal, State, and/or local authorities of reports of possible inappropriate prescribing or dispensing of Palladone.*

   PPLP response:
   We agree to provide the FDA with reports in the RADARS System Supplemental Report Focused on Hydromorphone, provided at 6 month intervals during the period of the phased launch and annually thereafter, of the number and types of actions taken by PPLP with regard to referral of practitioners to any federal , state, and /or local authority.

   Discussion
   See above comments for items 2 and 3. FDA seeks reporting on at least a quarterly basis.

7. *Detailed information about the elements of the RMP aimed at educating prescribers regarding the identification of patients who are at risk for developing addiction, and your efforts to minimize those risks.*

   PPLP response:
   As outlined in the Proposed Limited Rollout Document and the June 7, 2004 PPLP response, a packet of risk management education materials (Palladone Capsules Prescriber Packet) will be provided to prescriber on every initial sales call. The packet may include, but is not limited to, the following:

   ( )

   Discussion
   The Agency stated that the Sponsor's submission, dated May 5, 2004, stated that they will submit all promotional materials to DDMAC for review at least 2 weeks prior to actual use, for the first 6 months following product launch. In addition, courtesy copies will be sent to DDMAC for the next 12 months, 2 weeks prior to actual use. DDMAC stated that a proposed 2 week turn around for advisory comments is not sufficient. The complexity and quality of the promotional

materials are some of the factors that affect the timeframe in which advisory comments are provided. In general, an internal 15 business day turn around is reserved for core promotional materials such as a detail aid and journal ad. Other promotional materials will likely take a longer period of time. DDMAC advised the Sponsor to plan for this when anticipating a submission of advisory promotional materials. Therefore, DDMAC requested that the Sponsor propose a more adequate time frame for the review of all promotional materials for the first six months following product launch. Furthermore, DDMAC advised the Sponsor not to submit courtesy copies prior to actual use. The Sponsor should either submit the promotional materials for advisory review or submit them on a 2253 form (in duplicate) upon initial dissemination. The Sponsor agreed to revise their timeframe for submission of this material.

8. *Additional details about your proposed roll-out plan and how you will implement this plan over its various phases to assure that the plan meets your goals.*

PPLP response:
Details regarding the proposed Limited Rollout were outlined in the Proposed Limited Rollout Document, and in the June 7, 2204 and July 13, 2004 PPLP response. We will be glad to meet with you at your earliest convenience to provide any additional details of the rollout plan that the Agency may require.

Discussion
The Agency stated that more frequent reporting needed to be sent to the Agency during the rollout. The Sponsor agreed to work closely with the Agency to determine the best course of action and whether other reporting would be needed in addition to the options discussed and generally agreed to in the meeting for monthly and quarterly reporting as previously described.

Action Items

1. The Agency will meet with the review team to discuss the reporting options discussed during the meeting and will discuss this outcome with the Sponsor in the immediate future.

2. The Sponsor will provide the references supporting the use of the term — ' in the label.

3. The Sponsor will provide new language for the package insert concerning the use of the term —

4. The Sponsor will propose a plan concerning submission of the information from the EAB.

5. The Sponsor will propose a time frame for submitting information about early interventions.

6. The Agency will suggest preferred formats to the Sponsor for reporting data to the Agency on surveillance activities. The Agency will work with the Sponsor soon after approval to determine a meaningful and efficient data reporting format for items being reported to the Agency on a monthly or quarterly basis.

7. The Sponsor will propose a more adequate timeframe for the review of all promotional materials for the first six months following product launch.

Post Meeting

Below are the references requested by the Sponsor.

Brands, B., Blake, J., Sproule, B., Gourlay, D., and Busto, U. Prescription Opioid Abuse in Patients Presenting for Methadone Maintenance Treatment. *Drug and Alcohol Dependence* 2004, 73:199-207.

Fishbain, D.A., Rosomoff, H.L.,and Rosomoff, R.S. Drug Abuse, Dependence, and Addiction in Chronic Pain Patients. *Clin. J. Pain*, 1992, 7:77-85

Manchikanti, L., Pampati, V., Damron, R. N., Beyer C. D., Barnhill, R.C., and Fellows, B. Prevalence of Prescription Drug Abuse and Dependency in Patients with Chronic Pain in Western Kentucky. *J Ky Med Assoc.* 2003, 101: 511-517.

Saper, J. R., Lake III, A. E., Hamel, R.L., Lutz, T.E., Branca, B., Sims, D.B., and Kroll, M.M. Daily Scheduled Opioids for Intractable Head Pain. Long Term Observations of a Treatment Program. *Neurology,* 2004, 62:1687-1694.

Hoffman, N. G., Olofsson, O., Salen, B., and Wickstrom, L., Prevalence of Abuse and Dependency in Chronic Pain Patents. *The International Journal of the Addiction*, 1995, 30(8): 919-927.

Savage, S.R., Assessment for Addiction in Pain-Treatment. *The Clinical Journal of Pain* 2002, 18:S28-S38

Savage, S.R., Opioid therapy of Chronic Pain: Assessment of Consequences. *Acta Anaesthesiol Scand,* 1999, 43:909-917

Cowan D.T., Wilson-Barnet J., Griffiths P., Allan, L.G., A survey of Chronic noncancer pain patients prescribed opioid analgesics. *Pain Medicine,* 2003 Vol 4 #4 340-351

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/s/

Sara Stradley
9/10/04 01:45:41 PM

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

DATE: September 9, 2004

TO: Bob A. Rappaport, M.D., Director
Division of Anesthetic, Critical Care and Addiction Drug Products,
HFD-170

FROM: Paul Seligman, M.D., M.P.H, Director
Office of Pharmacoepidemiology and Statistical Science
(OPaSS), HFD-030

Anne Trontell, M.D., M.P.H., Deputy Director
Office of Drug Safety
(ODS), HFD-400

DRUG: Palladone® (Hydromorphone HCl Extended-Release Capsules)

NDA #: 21-044

SPONSOR: Purdue Pharma, L.P.

SUBJECT: Review of Revised Risk Management Plan submitted July 23, 2004

PID #: D040324

ODS Review of July 23, 2004 Purdue Submission in Relation to
July 16, 2004 Approvable Letter
Palladone® (hydromorphone HCL ER) (NDA 21-044)

1. **FDA Comment:**
We have reviewed and revised your proposed labeling. The revised labeling is enclosed. Prior to approval, you must submit revised draft labeling for the drug that is identical in content to the enclosed labeling. If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

PPLP Response:
See attachments 2-4 for revised draft labeling for this product as requested. The PI is provided as a red-line strikeout version (Attachment 2) using the document you sent to us

on July 16, 2004, as well as an annotated red-line strikeout version (attachment 3), and a clean version (attachment 4).

ODS Response: None

2. **FDA Comment:**
Pursuant to 21 CFR Part 208, FDA has determined that Palladone poses a serious and significant public health concern requiring distribution of a Medication Guide. Palladone is a drug product for which patient labeling could help prevent serious adverse effects. Palladone has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or to continue to use, the product. Palladone is important to health, and patient adherence to directions for use is crucial to the drug's effectiveness. The Medication Guide for NDA 21-044 Palladone should address concerns about overdose, addiction, and proper use. In accordance with 21 CFR 208.24, you will be responsible for ensuring the following:

   a. That a Medication Guide for Palladone is available for every patient who is dispensed a prescription for Palladone.

      PPLP response:
      See attachments 2-4 for a draft Medication Guide for Palladone. In order to make this medication Guide available for everyone patient dispensed a prescription for Palladone, we propose to provide this Medication Guide using some or all of the following methods:
      - To make med guide available in appropriate format to vendors who provide electronic information about drugs to retail pharmacies for the purposes of accompanying information in the prescription dispensing process.
      - To make a copy of the med guide available on our website in an easily downloadable format.
      - To provide adequate numbers of hard copies (e.g. tear pads) in every wholesale order that is shipped. Wholesalers, in turn, can forward these tear pads with each retail order.
      - To provide tear pads of the med guide to any HCP upon request.

   ODS response:
   DSRCS is reviewing the MedGuide under a separate consult.

   FDA Comment:
   b. That the label of each container of Palladone includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom Palladone is dispensed.

      PPLP response:

See attachment 5 for revised container labels that contain the requested instruction.

ODS response: None

FDA Comment:

c. That the label of each container includes a statement about how the Medication Guide is provided.

PPLP response:

See attachment 5 for revised container labels that indicate that meds guides accompany the product container.

ODS response: None

In addition, the following issues have yet to be resolved. You have agreed to implement a risk management plan (RMP) to ensure the safe use of the product post-approval. We would like to have further discussions with you regarding the following issues with your RMP, which remain unresolved:

1. **FDA Comment:**
   Establishing a baseline for current hydromorphone exposure, using information collected as part of Purdue's current active surveillance systems. This baseline information and any subsequent changes will allow for the assessment of the utility and value of your proposed surveillance tools as part of the Palladone RMP.

   PPLP Response:
   Reference is made to the RADARS System Supplemental Report Focused on Hydromorphone that was submitted in correspondence dated July 13, 2004. This report contains the baseline information that is available through Purdue's current active surveillance systems.

   ODS response:
   Ongoing surveillance using RADARS® will provide more timely data. Because different investigators report at differing frequencies (e.g. some monthly, some less frequently), we recommend that the sponsor provide separate rates for the regular and intermittent reporters as well as overall rates for each RADARS surveillance group.

2. **FDA Comment**
   Timely analysis of safety issues, including overdose and deaths, related to Palladone and how FDA may be notified of these issues. For instance, it would be useful to include the following postmarketing adverse event reports as 15-day "Alert Reports," in addition to those required to be reported under 21 CFR 314.80(c)(1)(i):
   a. All overdoses and deaths associated with Palladone

b. All reports of abuse, addiction, and misuse associated with Palladone
c. All adverse events and reports of exposure to Palladone involving children 18 years of age or younger
d. All adverse events occurring in "opioid-naïve" persons who use Palladone
e. All medication errors associated with the administration of Palladone

PPLP Response:
We agree that timely analysis of safety issues is important with any new product's market introduction. In response to the categories of particular interest cited above, we proposed submitting the information requested in items a through e in the Quarterly Periodic Reports that are required to be submitted to the FDA for the first three years following approval of Palladone. All postmarketing adverse events that have been received within the reporting period will be included in this report. In these Quarterly Periodic reports, we will provide specific listings of adverse events that fall within these five areas identified by FDA as being of particular interest.

ODS Response:
Members of the Office of Drug Safety, along with members of HFD-170 and the Controlled Substances Staff, met with representatives of Purdue Pharma on August 30, 2004 to discuss various aspects of the proposed Risk Management Plan. At that meeting, the firm noted that 15-day expedited reports for the above-mentioned events might not be logistically feasible. We have considered various options for reporting of these events, and have reviewed these with HFD-170 and the Controlled Substances Staff. Upon further evaluation, we recommend that the sponsor submit full case reports on a monthly basis, instead of on a 15-day expedited basis, that will include the following:

a. Labeled overdoses and deaths associated with Palladone
b. Reports of abuse, addiction, and misuse associated with Palladone
c. Adverse events and reports of exposure to Palladone involving children 18 years of age or younger
d. Adverse events occurring in "opioid-naïve" persons who use Palladone
e. Medication errors associated with the administration of Palladone
f. Reports of documented safety concerns identified via surveillance methods by geographical area

For ease of review, case reports (for items a through e above) should be submitted on MedWatch forms. It is suggested that the cut-off date be the end of the calendar month. All reports of items a through f above that are in your possession at the end of the calendar month should be submitted within 2 weeks of that cut off date. As agreed upon during the August 30, 2004 meeting, the monthly report will contain no data analysis. However, the data should be sorted and separated into categories. The monthly reports should be sent to the NDA and 4 desk copies sent to the Office of Drug Safety, and one desk copy to the Controlled Substance Staff. A meeting should be scheduled with the sponsor post-approval to work out the format of the monthly

reports. This plan was agreed upon internally, and was suggested in a letter sent to the Sponsor on September 8, 2004.

The Sponsor agreed to explore and propose mechanisms and timing for capturing and reporting to FDA items a through e that are not associated with adverse events, for instance medication errors.

In addition to the monthly reports, the Sponsor must also submit the 15-day alert reports and quarterly reports as stated in 21CFR314.80(c)(1)(i) and 21CFR314.80(c)(2) respectively.

The rationale for monthly reporting of the above mentioned adverse events (deaths, pediatric AEs, and medication error reports) is to 1) help detect early signals of problems related to inappropriate use or medication errors; and 2) may provide qualitative data on circumstances leading to deaths.

3. **FDA Comment:**
Timely submission of RADARS reports as well as reports from other surveillance mechanisms (e.g., DAWN, NSDUH, pertinent product inquiries, and media/medical literature surveillance) to FDA on a regular and frequent basis would facilitate evaluation of your RMP

PPLP response:
As indicated previously, please refer to the RADARS System Supplemental Report Focused on Hydromorphone submitted in correspondence dated July 13, 2004. We will provide FDA with similar reports on Palladone and other hydromorphone products at 6 month intervals during the period of the phased launch and annually thereafter. Information from DAWN, NSDUH, pertinent product inquiries, and media/medical literature surveillance will be included in these reports as new data become available. Time is specifically set aside at each of the quarterly meetings of the EAB during which newer data are presented to representatives of Federal Agencies, including FDA.

ODS response:

- ***Submit in your periodic report which is submitted quarterly, the RADARS reports as well as reports from other surveillance mechanisms (e.g., DAWN, NSDUH, pertinent product inquiries, and media/medical literature surveillance).***
    - ***These reports should include a complete description of any and all new analytical methods (e.g., new techniques for calculating denominators) that are under exploration.***
    - ***Please refer to the information below which outlines the type of information needed regarding the prescription report, surveillance reports from RADARS and the summary of interventions.***
- ***The Sponsor will propose data that will be sent to FDA without analysis on a quarterly basis, but with analysis every other quarter (6 months). Candidate data discussed at the August 30, 2004 meeting included the following:***
    - ***EAB meeting minutes and data presented***

- ***Data generated by the field forces in response to company SOPs and reporting of PPLC General Counsel suspicious reports, in tabular format***
- ***Supply chain loss report***
- ***Rx Patrol***
- ***Media Surveillance***
- ***RADARS quarterly data, to include line items (without analysis every other quarter)***
- ***Interventions undertaken and known consequences/impacts reported on a qualitative basis.***

ODS would like the opportunity to discuss with the Sponsor the optimal format and content of the monthly and quarterly reports to the Agency. A starting point for discussion might be the following:

A. Information on relevant adverse events

B. Prescription Report:
- Number of prescriptions
- Number and percentage attributed to prescriber specialty
- Prior therapy report
  - Numbers receiving opioid therapy prior to Palladone®
- Inappropriate prescribing report

C. Surveillance reports from RADARS® and data from national databases (e.g. DAWN, NSDUH)
- Reports need to include rates for consistent reporters

D. Proposed summary of interventions for Palladone® RMP

[ ]

4. **FDA Comment:**
Modification of your RMP to provide for the submission, within 15 calendar days of identification, of all reports documenting safety concerns by geographical area that are identified via any surveillance methodologies.

PPLP response:
How we will usefully report specific safety concerns by geographical area will require additional discussion.

ODS response:
Based on discussion, ODS will consider it acceptable to receive all documented or otherwise verified signals (as defined by the Sponsor in the RMP) of abuse, misuse or diversion that are identified via any surveillance methodologies for geographical areas defined as 3 digit zip codes as part of the monthly data reports (see item 2). This information should additionally be summarized in the quarterly reports.

5. **FDA Comment:**
Timely reporting to FDA of any interventions you initiate in response to the adverse event information you receive related to Palladone, and how you plan to (1) assess the results of these interventions and (2) apprise FDA of the results.

PPLP response:
In the RADARS System Report Focused on Hydromorphone, provided at 6 month intervals during the period of the phased launch and annually thereafter, we will provide a listing of interventions initiated in response to hydromorphone signals, as described in the updated RADARS System Report submitted to our OxyContin Controlled Release Tablets NDA 20-553 on June 18, 2004 along with our plans to assess the results of these interventions and apprise FDA of the results.

ODS response:
Submit in your periodic report which is submitted quarterly, the details of all interventions that would be initiated in response to instances of misprescribing, drug abuse, misuse, overdose, diversion, and deaths related to Palladone as well as the outcomes of those interventions including updates. More detail regarding the intervention and its impact or outcome is needed (than was provided in recent report) to help determine the effectiveness of specific intervention, i.e. whether signals diminish. Please refer to the table under ODS response #3, item C which provides an example of the type of information needed regarding each intervention.

6. **FDA Comment:**
Notification to FDA of instances where you have officially communicated with other Federal, State, and/or local authorities of reports of possible inappropriate prescribing or dispensing of Palladone.

PPLP response:
We agree to provide the FDA with reports in the RADARS System Supplemental Report Focused on Hydromorphone, provided at 6 month intervals during the period of the phased launch and annually thereafter, of the number and types of actions taken by PPLP with regard to referral of practitioners to any federal , state, and /or local authority.

ODS response:
This information should be provided in your periodic report which is submitted quarterly.

7. **FDA Comment:**
Detailed information about the elements of the RMP aimed at educating prescribers regarding the identification of patients who are at risk for developing addiction, and your efforts to minimize those risks.

PPLP response:
As outlined in the Proposed Limited Rollout Document and the June 7, 2004 PPLP response, a packet of risk management education materials (Palladone Capsules Prescriber Packet) will be provided to prescriber on every initial sales call. The packet may include, but is not limited to, the following:

[redacted]

ODS response:
Final materials submitted to the Agency should include this content. The use of the Medication Guide, that contains risk information, and health care provider materials, that include information about identifying patients who are at risk for developing addiction, are adequate educational efforts to address the risk of patients developing addiction.

8. **FDA Comment:**
Additional details about your proposed roll-out plan and how you will implement this plan over its various phases to assure that the plan meets your goals.

PPLP response:
Details regarding the proposed Limited Rollout were outlined in the Proposed Limited Rollout Document, and in the June 7, 2204 and July 13, 2004 PPLP response. We will be glad to meet with you at your earliest convenience to provide any additional details of the rollout plan that the Agency may require.

ODS response (not discussed in sponsor meeting on August 30, 2004):
- ***Regarding the proposed limited rollout plan, ODS recommends the use of an evaluation metric to assess moving from one phase to the next of the limited rollout plan. FDA would appreciate the opportunity to review such data.***
- ***The Agency would like to be informed about the decision-making process related to expansion of the rollout.***
- ***ODS recommends the Sponsor include in the revised plan a complete description of how inappropriate prescribers will be identified during the limited rollout;***

including details on the criteria by which they will identify these individuals. Please refer to the June 7, 2004 update where reference is made to the use of select criteria to identify inappropriate prescribers.

- ***ODS recommends the Sponsor include in the revised plan a provision for timely reporting to the Agency (e.g. six months prior to the anticipated cessation of the limited rollout), the data and analysis of the evaluation metrics used to assess the rollout. This timing will allow the Agency to perform its own review of the data and obtain as necessary input from appropriate outside experts and/or to gain Advisory Committee input on the impact of the program's performance on product safety.***

Additional ODS Comments:

Drug utilization analyses

- *When providing the prior therapy report please provide step by step detailed calculations of how estimates of prior therapy were obtained, so they can be interpreted appropriately, in particular how accurately "opioid naïve" patients are identified and verified.*

ODS RMP Review Team:
Gerald Dal Pan, MD, MHS, Director, DSRCS /s/ 9-9-04
Mary Dempsey, Project Management Officer, ODS /s/9-9-04
Claudia B. Karwoski, Pharm.D, Scientific Coordinator (Detail), ODS /s/ 9-9-04
Mary Willy, PhD, Epi Team Leader, DDRE /s/ 9-8-04

_____
Anne Trontell, M.D., M.P.H., Deputy Director
Office of Drug Safety (ODS), HFD-400

_____
Paul Seligman, M.D., M.P.H, Director
Office of Pharmacoepidemiology and Statistical Science (OPaSS), HFD-030

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/s/

Mary Dempsey
9/9/04 05:27:48 PM
DRUG SAFETY OFFICE REVIEWER

Anne Trontell
9/9/04 05:31:06 PM
DRUG SAFETY OFFICE REVIEWER

Paul Seligman
9/9/04 05:46:10 PM
UNKNOWN

MEMORANDUM

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

DATE: September 9, 2004

TO: Bob Rappaport, M.D., Director
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

VIA: Sara E. Stradley, Regulatory Health Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

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: DSRCS Review of Medication Guide for Palladone™ (hydromorphone HCl extended-release) Capsules, NDA 21-044.

Background and Summary

The patient labeling (marked copy) which follows represents the revised Medication Guide for Palladone™ (hydromorphone HCl extended-release) Capsules, NDA 21-044. It has been reviewed by DSRCS 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), 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 by the sponsor in July 23, 2004. Patient information should always be consistent with the prescribing information. All future changes to the PI should also be reflected in the PPI.

Comments to the review Division are bolded, italicized, and underlined. We can provide a Word copy of the revised document if requested by the review division. Please let us know if you have any questions.

7 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

Jeanine Best
9/9/04 02:40:31 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
9/9/04 03:09:39 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-044

INFORMATION REQUEST LETTER

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

9/8/04

Attention: Richard J. Fanelli, Ph.D.
Senior Director

Dear Dr. Fanelli:

Please refer to your December 28, 1998 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Palladone (hydromorphone hydrochloride extended-release) Capsules.

We also refer to your submission dated July 23, 2004 and the meeting held between representatives of your company and the Agency on August 30, 2004 to discuss the issues identified in the July 16, 2004 action letter.

We have the following additional comments concerning the Agency's request for 15-day reports as stated in the July 16, 2004 action letter.

Upon further evaluation, we recommend that you submit full case reports on a monthly basis, instead of on a 15-day expedited basis, that will include the following:

a. Labeled overdoses and deaths associated with Palladone

b. Reports of abuse, addiction, and misuse associated with Palladone

c. Adverse events and reports of exposure to Palladone involving children 18 years of age or younger

d. Adverse events occurring in "opioid-naïve" persons who use Palladone

e. Medication errors associated with the administration of Palladone

f. Reports of documented safety concerns identified via surveillance methods by geographical area

For ease of review, these line listings should be placed on MedWatch forms. It is suggested that the cut-off date be the end of the calendar month. All reports of items a through f above that are in your possession at the end of the calendar month should be submitted within 2 weeks of that cut off date. As agreed upon during the August 30, 2004

meeting, the monthly report will contain no data analysis. However, the data should be sorted and separated into categories. The monthly reports should be sent to the NDA and 4 desk copies sent to the Office of Drug Safety, and one desk copy to the Controlled Substance Staff.

In addition to the monthly reports, you also need to submit the 15-day alert reports and quarterly reports as stated in 21CFR314.80(c)(1)(i) and 21CFR314.80(c)(2) respectively.

If you have any questions, call Sara E. Stradley, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Supervisory CSO
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Parinda Jani
9/8/04 12:50:33 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

8/5/04

NDA 21-044

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Richard J. Fanelli, Ph.D.
Senior Director, US Regulatory Affairs

Dear Dr. Fanelli:

We acknowledge receipt on July 26, 2004 of your July 23, 2004 resubmission to your new drug application for Palladone (hydromorphone hydrochloride extended-release capsules).

We consider this a complete, class 1 response to our July 16, 2004 action letter. Therefore, the user fee goal date is September 26, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the deferral granted on September 13, 2002 for the pediatric study requirement for this application.

If you have any question, call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara Stradley, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sara Stradley
8/5/04 08:31:08 AM

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: July 16, 2004

To: Bob A. Rappaport, M.D., Director
Division of Anesthetic, Critical Care
and Addiction Drug Products (HFD-170)

From: Silvia N. Calderon, Ph.D., Team Leader
Controlled Substance Staff (HFD-009)

Subject: Consultation regarding proposed Risk Management Program
NDA 21-044, Palladone Extended Release Capsules
Sponsor: Purdue Pharma L.P.
Submission reviewed in this consult: May 17, 2004; correspondence dated May 21, 2004.

BACKGROUND

This memorandum responds to the Division of Anesthetic, Critical Care, and Addiction Drug Products's request for CSS consultation on the Palladone's RMP dated May 17, 2004.

Regarding Palladone's RMP, CSS's prior consultations (September 26, 2001 and September 12, 2002) included several recommendations to be addressed by the Sponsor at the time of the resubmission of the NDA.

Prior RMP submissions were dated July 17, 2001; July 2, 2002; September 9, 2002, December 23, 2002, March 12, 2003, a follow up meeting with the Sponsor on June 23, 2003 and the Anesthetic and Life Support Drugs Advisory Committee's recommendation on September 9-10, 2003. As part of the current RMP submission, the Sponsor presents information on their proposed rollout plan and metrics in response to the Anesthetic and Life Support Drugs Advisory Committee's (September 9-10, 2003) recommendation, subsequent meeting with FDA on December 17, 2003, and a follow-up telecom on February 12, 2004.

Evaluation and recommendations regarding the rollout plan and metrics were provided to the Division in consult dated May 19, 2004. At the June 28, 2004 internal review team meeting, CSS provided the Division with recommended changes to the label.

COMMENTS

- The Palladone RMP is very similar to the OxyContin RMP, which has not yet been evaluated as an effective plan in reducing oxycodone related mortality and abuse

- Although the Sponsor collected information on the abuse and misuse of hydromorphone as part of the current OxyContin RMP, these data have not been submitted to the Agency.

- The Sponsor has committed to restricting the use of Palladone to opioid tolerant patients and revise key messages accordingly. Current key messages identify proper patient selection, revised indication, Schedule II control status, disposal of unused units, messages to prevent abuse of the product by the household members and safety messages associated with crushing, chewing or dissolving of the formulation.

- The Sponsor incorporated the use of physician-patient written agreements and informed consent for treatment as part as their educational materials.

- In response to prior questions regarding the determination of the prevalence of iatrogenic addiction, the Sponsor had proposed a pilot study for the "Prospective Study of Patients Suffering from Chronic Pain" in prior RMP proposals. This study is not mentioned in current RMP proposal.

- The Sponsor did not outline a timeline for submission of reports of abuse, misuse, overdose and diversion to FDA. Instead the Sponsor proposed that reports of abuse, misuse, overdose and diversion collected by the four RADAR's data sources will be reported to the EAB on a quarterly basis and that final reports of these data will be submitted to FDA annually.

- The RADARS system has currently identified at least two areas with high rates of hydromorphone abuse in 2002. No information has been submitted to FDA that will help to understand and evaluate the scope of the problem.

RECOMMENDATIONS

1. Provide information collected as part of Purdue's active surveillance system (DAWN, NSDUH, Spontaneous Adverse events and RADARS) on the incidence of hydromorphone abuse, addiction, misuse, diversion and deaths. Hydromorphone should be the focus of the analysis. This information will help Purdue and FDA to assess the levels of abuse, misuse, overdose and deaths before the introduction of Palladone in order to establish a baseline.
   It is necessary for the Agency to review the experience and success of the RADARS program and other proposed surveillance tools to detect clusters of abuse, misuse,

diversion and death of currently marketed prescription opioids in order to assess their potential utility and value in the Palladone RMP.

2. The Sponsor did not outline a timeline for submission of reports of abuse, misuse, overdose, diversion and deaths to FDA.

   We restate our prior recommendation that drug abuse, misuse, overdose, diversion events, and deaths should be reported as 15-day reports to FDA, with the exception of those reports identified through the Key Informant Network that might be reported quarterly.

   In addition, all reports documenting geographical areas of abuse, misuse or diversion identified via any surveillance methodology should be reported to the Agency within 15 calendar days of identification

3. The Sponsor should specify what additional prevention tools will be implemented to avoid misuse, abuse, diversion and hydromorphone related deaths when marketing Palladone in areas where the RADARS system has already identified high rates of hydromorphone abuse. Some questions that need to be addressed include, how Palladone will be marketed in those areas, how will it be promoted and regional educational efforts.

4. The Sponsor should provide information on their initiative to educate prescribers to identify patients at risk of developing addiction and minimize those risks. In addition, the RMP should address reporting on the rate of patients who became addicted in the course of chronic pain treatment (iatrogenic addiction) to tailor educational and other potential intervention programs.

5. Evaluation of the rollout phase and report of the findings before expanding the detailing and marketing of the product.

6. Convert the Patient Package Insert to Medication Guide to assure that every patient will receive appropriate information on the safe use of Palladone with each prescription.

7. Report interventions initiated in response to instances of misprescribing, drug abuse, misuse, overdose, diversion events, and deaths. Report the outcome of those interventions.

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/s/

Silvia Calderon
7/16/04 12:02:33 PM
CHEMIST

Silvia Calderon
7/16/04 12:04:57 PM
CHEMIST

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)827-7410

DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVABLE ACTION

DATE:	July 16, 2004
DRUG:	Palladone™ (hydromorphone HCl extended-release capsules, 12 mg, 16 mg, 24 mg and 32 mg)
NDA:	21-044
NDA Code:	Type 3S NDA
SPONSOR:	Purdue Pharma, L.P.
INDICATION:	For the management of persistent moderate to severe pain in patients requiring continuous, around-the-clock opioid analgesia with a high potency opioid for an extended period of time [ ]

NDA 21-044 was submitted by Purdue Pharma, L.P. in support of their extended-release formulation of hydromorphone on December 29, 1998. Upon review of the initial application, the Division determined that the clinical studies did not provide adequate evidence of efficacy. An approvable letter was issued on December 29, 1999, that requested submission of at least one additional adequate and well-controlled study, as well as changes to the dissolution specifications, certification of child-safe packaging, and resolution of nomenclature concerns. A complete response was submitted on March 30, 2001. Upon review of that submission, the Division determined that the new study that had been submitted did not provide adequate evidence of efficacy. Additionally, methodological deficiencies and issues of data integrity identified during inspection of study sites used for that trial did not allow the use of the data as the primary basis for an approval decision. A non-approvable letter was issued on October 4, 2001. In addition to requiring submission of another adequate and well-controlled clinical trial in support

of efficacy, the letter noted that further data regarding product stability would also be required at resubmission.

A complete response to the non-approvable letter was received on March 12, 2002. That submission included data from a multiple-dose efficacy study in patients with chronic pain. Upon review of that submission, including all safety data and safety updates, the Division found that the sponsor had, indeed, provided evidence that Palladone was safe and effective when used appropriately. In addition, adequate stability data had been provided. However, inspection of the manufacturing site for the finished dosing form found significant new GMP deficiencies, in addition to unresolved deficiencies from previous inspections. The Office of Compliance issued a Withhold Approval recommendation. Thus, a second approvable letter was issued on September 13, 2002. In addition to the requirement for resolution of the GMP deficiencies upon reinspection, this letter noted deficiencies related to drug substance specifications needing resolution and a requirement for qualification of the genotoxic potential of the drug substance impurity morphinone due to a recent structural alert determination by the Division.

Finally, the second approvable letter noted the following:

> While not specifically a condition of approval, agreement on the elements of the Risk Management Program designed at minimizing the risk of abuse and diversion of this product should be resolved before this product is marketed.

On September 9 and 10, 2003, the Anesthetic and Life Support Drugs Advisory Committee held an open public meeting to discuss RMP's for opiate analgesics, with particular attention to modified-release products, and a proposed RMP for Palladone. The committee concurred with the Division's assessment that Palladone was likely to be a target of abuse and that a carefully crafted RMP was essential in any attempt to reduce this risk. The sponsor proposed a limited rollout plan for promotion that could be assessed at various points before moving from one phase of the plan to the next. While the committee found this program to be generally worthwhile, they did recommend that the time course for the rollout be extended.

On December 17, 2003, the Division and representatives from the Office of New Drugs, the Office of Drug Safety, the Controlled Substances Staff, and the Center Director's Office met with the sponsor to discuss the outcomes of the advisory committee meeting and the company's plans for further development of the RMP. The Agency representatives clearly outlined our expectations for a thorough and complete RMP and an appropriately designed limited rollout phase for promotion of Palladone.

A complete response to the September 13, 2002 letter was received on May 17, 2004. This submission consists of evidence documenting that the GMP deficiencies at the Totowa manufacturing site have been adequately addressed, and includes a proposed final RMP and proposed final product labeling. In addition, the response includes the reports of the required genotoxicity studies on the morphinone impurity.

The genotoxicity studies were reviewed by Suzanne R. Thornton-Jones, Ph.D. Dr. Thornton-Jones found that morphinone besylate was not mutagenic in the in vitro Ames bacterial reversion assay or clastogenic in the in vivo mouse micronucleus assay. However, morphinone besylate was clastogenic in the Chinese Hamster Ovary chromosomal aberration assay both with and without metabolic activation. While the sponsor's current specification for the impurity is not adequate based on the above finding, as previously agreed upon, we will work with them during Phase 4 to assure reduction of this specification to an acceptable level in a timely manner.

After extensive review of the proposed RMP, including consultation with the Controlled Substances Staff and the Office of Drug Safety, the Division has determined that, while the current draft represents a significant advance over earlier iterations, further changes and additions will be necessary before we are able to conclude that the plan is adequate to assure the safe marketing of Palladone. These changes and additions include:

- The submission of all data regarding abuse, misuse, overdose, addiction or diversion associated with hydromorphone, from RADARS and other surveillance programs, and appropriate analyses of that data

- The submission of a plan for submitting reports of abuse, misuse, overdose, diversion and deaths associated with Palladone or other hydromorphone-containing products

- The submission of a plan that describes how interventions will be reported to the Agency

- The submission of a detailed plan for educating prescribers regarding the potential for addiction in patients treated with Palladone

- The submission of a Medication Guide

- The submission of a plan to address hydromorphone-associated abuse, misuse, and addiction in geographical regions already showing a signal of one or the other of these concerns

- The submission of a specific timeline that addresses all features of the limited rollout, to include adequate opportunity for Agency review and feedback.

Action: Approvable

Bob A. Rappaport, M.D.
Director
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II, CDER, FDA

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/s/

Bob Rappaport
7/16/04 07:38:15 PM
MEDICAL OFFICER

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

DATE: July 14, 2004

TO: Bob A. Rappaport, M.D., Director
Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170

THROUGH: Paul Seligman, M.D., M.P.H, Director
Office of Pharmacoepidemiology and Statistical Science
(OPaSS), HFD-030

Anne Trontell, M.D., M.P.H., Deputy Director
Office of Drug Safety
(ODS), HFD-400

FROM: Gerald Dal Pan, MD, MHS, Director,
Division of Surveillance, Research and Communication Support
(DSRCS), HFD-410

Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support
(DMETS), HFD-420

Mark Avigan, MD, MPH, Director
Division of Drug Risk Evaluation
(DDRE), HFD-430

DRUG: Palladone® (Hydromorphone HCl Extended-Release Capsules)

NDA #: 21-044

SUBJECT: Review of Revised Risk Management Plan submitted May 18, 2004

PID #: D040324

EXECUTIVE SUMMARY

At the request of the Division of Anesthetic, Critical Care, and Addiction Drug Products (DACCADP), the Office of Drug Safety (ODS) reviewed the most recent revised risk management plan (RMP) for Palladone® (hydromorphone HCl extended-release capsules) submitted by Purdue Pharma as part of its new drug application (NDA 21-044). Palladone™ Capsules are an opioid analgesic available in 12 mg, 16 mg, 24 mg, and 32 mg capsule strengths

and are indicated for the management of persistent, moderate to severe pain in **opioid-tolerant** patients requiring continuous, around-the-clock opioid analgesia for weeks or longer.

The Palladone™ RMP utilizes healthcare professional and patient education, planned surveillance/intervention activities, and a launch plan they term a "limited rollout", which is a new element of the proposed RMP. The launch plan [redacted]. The patient package insert has been reviewed in a separate document.[1]

Overall, the current RMP is improved over the previous draft submitted to the FDA. ODS has identified additional issues regarding the labeling, provider and patient education, surveillance and the launch of the product that should be addressed prior to approval of the product.

Labeling

We recommend that the package insert include a warning statement that informs practitioners and/or patients that the Palladone capsules should not be opened, and that all references to the alternative administration of the products [redacted] be deleted. The professional label suggests that ingesting chewed, dissolved, or crushed Palladone™ Capsules or its contents can lead to the rapid release and absorption of a potentially fatal dose of hydromorphone. The proposed removal of the reference to [redacted] from the product label is a step in the right direction. The potential risk of a fatal overdose should preclude ingesting this product in ways other than orally as an intact capsule.

Education Program

The educational program for healthcare providers should be more Palladone-specific by including safety messages specific to Palladone such as appropriate patient selection (only for opioid-tolerant patients with continuous pain requiring therapy for a few weeks or more). A Medication Guide should be distributed with this product (see CFR 21, Part 208) as it meets 2 of the 3 circumstances under which such a guide would be required. Finally, a plan for providing professional education to retail and hospital pharmacists should be developed that emphasizes the indications, warnings and precautions for Palladone.

Surveillance

An assessment by FDA of the ability of the Researched Abuse, Diversion, and Addiction–Related Surveillance (RADARS) system to detect clusters of abuse, misuse and diversion of currently marketed opioids, particularly hydromorphone, needs to be completed before a judgment can be made as to its appropriateness and value as a timely or sensitive surveillance tool for the safety risks associated with Palladone. Details of such an assessment are provided in the body of this review. Once satisfied that RADARS is an appropriate surveillance tool, product approval should include a provision for quarterly submission to the FDA of status reports of identified clusters of abuse, misuse, and diversion, and any interventions that have been initiated, beginning three months after launch of the product. Additionally, all

[1] Best, Jeanine. Review of Patient Labeling for Palladone®, dated June 23, 2004.

postmarketing adverse events that result in death, that are due to misuse or overdose, that involve use in children under the age of 18 years, or that involve a medication error should be required to be submitted to the agency as 15-day expedited reports.

A key deficiency of the current risk management program is the lack of systematic information-sharing of postmarketing safety information obtained through specialized pharmacovigilance such as RADARS, product inquiries, media and medical literature surveillance, DAWN, NSDUH, and others. These data should be shared with FDA at least quarterly and within 15 days of the quarter's closing. In instances where notification of Federal, State, or local authorities is occurring because of possible inappropriate prescribing or dispensing, FDA should be notified simultaneously of the location by 3-digit zip code, number of offending prescribers or facilities involved, and the amount of product or number of prescriptions involved. Such notification should include information on interventions initiated to address the identified safety concerns.

Launch Plan

The purpose of the launch plan is to educate providers with the highest frequency of prescribing single-entity opioids. The purpose is not to limit the availability of the drug. As no data are available to judge whether such a launch plan will have its intended effect of ensuring that prescribers are prescribing the product per its indications, a 12-month evaluation of the plan should be presented and discussed publicly at an Advisory Committee meeting. Criteria for conducting such an evaluation are provided below in the review. During the launch period, the sponsor should meet with their External Advisory Board (EAB) at least quarterly to ensure that the plan is meeting its stated objectives. Interim reports on the appropriateness of Palladone prescribing and use to its limited indication and population should be shared with FDA at least quarterly, and should be expedited to the Agency within 15 days in selected circumstances.

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

Mary Dempsey
7/15/04 01:52:49 PM
DRUG SAFETY OFFICE REVIEWER

Anne Trontell
7/15/04 01:55:26 PM
DRUG SAFETY OFFICE REVIEWER
Signed in representation of comments from the Office of Drug Safety

Paul Seligman
7/15/04 01:59:36 PM
UNKNOWN

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Section 1.01 DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-044

INFORMATION REQUEST LETTER

7/8/04

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Richard J. Fanelli, Ph.D.
Senior Director

Dear Dr. Fanelli:

Please refer to your December 28, 1998 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Palladone (hydromorphone hydrochloride extended-release) Capsules.

We also refer to your submissions dated May 17 and June 7, 2004.

The Office of Drug Safety (ODS) and Controlled Substance Staff (CSS) are reviewing the proposed Risk Management Plan (RMP) of your submission and they have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Regarding proposed surveillance activities:

   a. It will be necessary for the Agency to review the ability of RADARS and the other proposed databases to detect clusters of abuse, misuse, and diversion of currently marketed opioids in order to assess the value of these data sources as timely and sensitive surveillance sources. Therefore, we request that you submit the following items to NDA 21-044:

      (1) Supplement the RADARS System Report, originally submitted to NDA 20-553 for OxyContin Tablets, on June 18, 2004, with the following additional analyses:

         (a). Data (similar to that submitted in the RADARS System Report for NDA 20-553) on the nonmedical use of opioids (lifetime and current use). That data should specifically address hydromorphone (from NSDUH for all ages).

         (b). Any data from DAWN pertaining to the abuse and/or misuse of hydromorphone.

(c). Nationwide rates of abuse, misuse, addiction, diversion, etc. of hydromorphone, using all denominators examined to date from the Key Informant Network, the Law Enforcement Drug Diversion Network, the Poison Control Centers, the Drug Evaluation Network System (DENS), and the American Association for the Treatment of Opioid Dependence (AATOD).

(d). The 3-digit zip codes where signals for hydromorphone abuse, misuse, addiction, diversion, etc. have been identified.

(e). Any results obtained from the focused studies for OxyContin (OxyContin Use, Abuse and Diversion in Southwest Virginia; Illicit Opioid Use in Maine; and, Prescription Drug Use and Eastern Kentucky) that may have also identified problems with hydromorphone.

b. For RADARS to serve as an appropriate surveillance tool, submit a plan that assesses how frequently all data will be analyzed and how often those reports will be submitted to the Agency. Reporting this as an "ongoing" process without specific feedback points to FDA is not acceptable.

c. Submit a plan for timely reporting to the Agency when areas of abuse, misuse, or diversion are identified via any surveillance mechanism. Describe sources of the drug identified as abused and misused and how to differentiate between patient-abuse-addiction cases and cases involving street or diverted drug.

d. Provide further detail for the study proposed in your March 12, 2003 submission, titled "Prospective Study of Patients Suffering from Chronic Pain." The results of this study should help to identify patients and or prescribes at risk to tailor education and other potential intervention programs.

e. Submit a plan for timely reporting to the Agency when areas of abuse, misuse, or diversion are identified via any surveillance mechanism.

f. Submit a plan for timely reporting of any interventions that are initiated in response to these instances, and plans to address the outcome(s) of those interventions.

g. Describe how the data obtained through basic surveillance (i.e., DAWN, NSDUH, and spontaneous adverse events) will be utilized to assess risk and how often these analyses will be reported to the Agency.

h. Provide your rationale for removing the analysis of the Drug Evaluation Network System (DENS) from the signal detection studies.

i. Provide background information and describe the information that will be gathered from the American Association for the Treatment of Opioid Dependence study which you have added to the reporting plan.

j. In regard to surveillance, provide definitions currently in use, or to be used, to identify cases of abuse, misuse, addiction, diversion, overdose, and inadvertent pediatric exposure.

k. Provide your rationale for removing the analysis of Toxic Exposure Surveillance System (TESS) from the Palladone RMP.

l. Explain your rationale for changing the definition of a positive signal in the Rocky Mountain Drug and Poison Information Center to 2 cases/100,000 persons.

2. Regarding the proposed educational program:

a. Develop a comprehensive plan for providing professional education to retail and hospital pharmacists.

b. Change the educational program for healthcare providers so that it is more specific and includes safety messages directed towards Palladone, e.g., appropriate patient selection: "Only for opioid-tolerant patients with continuous pain requiring therapy for a few weeks or more."

c. Convert the Patient Package Insert to a Medication Guide.

3. Regarding the proposed limited rollout plan:

a. Describe your system to identify possible inappropriate prescribers, and describe the interventions (e.g., further education from sales representatives, notification to the DEA) that will be in place for those prescribers once they are identified. Additionally, describe how these inappropriate prescribers will be reported to FDA in a timely fashion.

b. Describe how patient provider agreements and patient education will be used during the limited rollout timeframe.

c. Identify the "other" prescriber specialties (by specific specialty) that will be targeted in [redacted] the limited rollout.

d. Explain your rationale for disproportionately expanding the rollout sales force from approximately [redacted] sales representatives in [redacted] to approximately [redacted] sales representatives in [redacted] (and using the same number of sales representatives in [redacted].

e. Provide information to document the availability and data characteristics of the "Prior Therapy Report" described in the Minimum Candidate Rollout-3A.

f. Provide a plan to update the FDA when new analytical methods (e.g., new techniques for calculating denominators) are explored.

g. Provide a plan for notifying/involving FDA in your decision-making to expand the rollout at each stage, based on the evaluation metrics.

If you have any questions, call Sara E. Stradley, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Supervisory CSO
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
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Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431
(203) 588 8000
Fax (203) 588 8850
www.purduepharma.com

July 1, 2004

DUPLICATE

Bob A. Rappaport, M.D., Director
Division of Anesthetic,
Critical Care and Addiction Drug Products
Office of Drug Evaluation II
Food and Drug Administration
HFD-170, Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

SUBMITTED IN DUPLICATE

GENERAL CORRESPONDENCE:
PEDIATRIC STUDY PLANS

N-000-C

NEW CORRESP

Re: Palladone™ (hydromorphone hydrochloride extended-release) Capsules
NDA #21-044

Dear Dr. Rappaport:

Reference is made to the Purdue Pharma L.P. (PPLP) New Drug Application #21-044 for Palladone™ (hydromorphone hydrochloride extended-release) Capsules submitted to the Agency on December 29, 1998, and to the amendments to this NDA dated March 30, 2001 and March 12, 2002. Reference is also made to the Division's approvable action letter dated September 13, 2002, to our responses dated October 4 and November 26, 2002, and to our resubmission dated May 17, 2004.

In addition, reference is made to our July 20, 2001 letter requesting a waiver for pediatric studies, and to your April 19, 2002 response in which the waiver request was denied. In that letter you acknowledged our intent to request a Written Request and recommended that we submit a pediatric plan for a modified formulation. On May 23, 2002, we submitted a letter requesting a deferral of the time to submit our request until after this NDA was approved.

In your approvable action letter of September 13, 2002 and again in your letter dated May 25, 2004 acknowledging receipt of our resubmission, you stated that pediatric studies are deferred until December 31, 2005. We will need to discuss the timing of this commitment, since given the extensive review period for this application, we will need additional time to address this request. We still intend to submit a request with our pediatric study plans shortly following NDA approval.

If you have any questions about this submission, please do not hesitate to contact me by telephone at (203) 588-8365, by fax at (203) 588-6229, or by electronic mail at richard.fanelli@pharma.com.

Sincerely,

Richard J. Fanelli, Ph.D.
Senior Director
U.S. 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

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Purdue Pharma L.P.	July 1, 2004
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(203) 588-8000	(203) 588-6229
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
One Stamford Forum Stamford, CT 06901-3431	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-044

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
hydromorphone hydrochloride	Palladone™ (hydromorphone hydrochloride extended-release) Capsules

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
4,5a - epoxy-3-hydroxyl-17-methylmorphinan-6-one-hydrochloride	HHER

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
capsules (extended release)	12, 16, 24 and 32 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

For the management of persistent, moderate to severe pain in patients requiring continuous, around-the-clock

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (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 N/A 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
General Correspondence: Pediatric Study Plans

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

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

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

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

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)* - **General Correspondence: Pediatric Study Plans**

CERTIFICATION

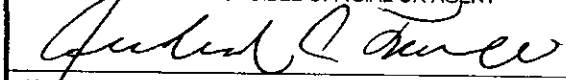
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. 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:
	Richard J. Fanelli, PhD. Senior Director, U.S. Regulatory Affairs	July 1, 2004

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
One Stamford Forum Stamford, CT 06901-3431	(203) 588-8365

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.

MEMORANDUM

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

DATE: July 1, 2004

FROM: Tara P. Turner, Pharm.D., Regulatory Project Manager
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: PISC Consideration of Medication Guide for Palladone™
(Hydromorphone HCl Extended-Release) Capsules

TO: NDA 21-044

The Patient Information Subcommittee (PISC) of the Medical Policy Coordinating Committee was asked to consider a medication guide for Palladone due to the following safety concerns raised by the OND review team, ODS, and the CSS staff:

1. Risk of hypoventilation in opioid naïve patients
2. Risk of accidental ingestion by children
3. Risk of overdose due to crushing, dissolving, or chewing the capsules

Due to the impact of a fast approaching action date of July 16, 2004, the PISC voting members (Bob Temple, Sandy Kweder, Anne Trontell) were consulted on this issue via e-mail. The three voting members concurred that a medication guide for Palladone is appropriate and can be discussed with the sponsor at this point. Please see their responses below. A formal discussion of this issue will take place at the next PISC meeting, which will be scheduled in the near future.

Please call us if you have any questions.

Attachment:

From: Temple, Robert
Sent: Monday, June 28, 2004 4:49 PM
To: Kweder, Sandra L; Trontell, Anne E
Cc: Turner, Tara; Rappaport, Bob A
Subject: RE: Possible medguide

Follow Up Flag: Follow up

Flag Status: Flagged
Agree.

-----Original Message-----
From: Kweder, Sandra L
Sent: Monday, June 28, 2004 4:17 PM
To: Trontell, Anne E; Temple, Robert
Cc: Turner, Tara; Rappaport, Bob A
Subject: RE: Possible medguide

I absolutely agree that a MedGuide is most appropriate for Palladone.

-----Original Message-----
From: Trontell, Anne E
Sent: Monday, June 28, 2004 2:26 PM
To: Kweder, Sandra L; Temple, Robert
Cc: Turner, Tara; Rappaport, Bob A
Subject: Possible medguide

Sandy and Bob,

The OND review team (including Bobs Rappaport and Meyer), ODS, and the CSS staff all feel there is merit to having a medication guide for Palladone. The action date is 7/16, tho the action is unresolved at this time. Looks like Bob R is going to try for an approvable or an extension to the clock in light of unresolved issues about the postmarketing safety surveillance in relation to the "limited rollout" proposed by the sponsor for this plan.

I told Bob R. that I thought the PISC would very likely approve this extended release hydromorphone product for a med guide with no objections, but that I would confirm that with both of you. It is risky for opioid naive patients, if you crush or chew it, or if it gets into the hands of children. Any objections?

If you agree that a Medication guide can be discussed with the sponsor for this product, I'd still suggest we go ahead and have a PISC meeting to consider it formally including dates after July 16 if necessary.

Thanks.

Anne

Anne Trontell, M.D., M.P.H.
Deputy Director
Office of Drug Safety
Center for Drug Evaluation and Research
15B-33 Parklawn
HFD-400
5600 Fishers Lane
Rockville MD 20857
301-827-3219
301-443-5161 (fax)
trontella@cder.fda.gov

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

/s/

Tara Turner
7/1/04 10:44:23 AM
UNKNOWN

6/29/04

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-044

INFORMATION REQUEST LETTER

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Richard J. Fanelli, Ph.D.
Senior Director, US Regulatory Affairs

Dear Dr. Fanelli:

Please refer to your December 28, 1998 submission, received December 29, 1998, of your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Palladone (hydromorphone hydrochloride extended-release capsules).

We also refer to your submission dated May 17, 2004 which constituted a complete response to our September 13, 2002 action letter.

The Division of Medication Errors and Technical Support (DMETS) and the Division of Drug Marketing, Advertising, and Communication (DDMAC) have reviewed the referenced materials and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The use of the proprietary name, Palladone, is acceptable.

2. Revise the established name in the blister foil label to read "capsule" rather than "capsules" as there is only one capsule in each blister.

3. Revise the font size of the area including the usual dosage and storage requirements on the container label.

If you have any questions, call Sara E. Stradley, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Supervisory CSO
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
6/29/04 02:08:37 PM

MEMORANDUM

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

DATE: June 23, 2004

TO: Bob Rappaport, M.D., Director
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

VIA: Sara E. Stradley, Regulatory Health Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

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 Palladone™ (hydromorphone HCl extended-release) Capsules, NDA 21-044.

Background and Summary

The patient labeling (marked copy) which follows represents the revised risk communication materials of the Patient Labeling for Palladone™ (hydromorphone HCl extended-release) Capsules, NDA 21-044. It has been reviewed by DSRCS 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), 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 by the sponsor in May 17, 2004. Patient information should always be consistent with the prescribing information. All future changes to the PI should also be reflected in the PPI.

Comments to the review Division are bolded, italicized, and underlined. We can provide a Word copy of the revised document if requested by the review division.

Comments on the sponsor's Risk Management Plan, submitted May 17 2004, will come separately, in an ODS combined document.

Please let us know if you have any questions.

Appears This Way
On Original

7 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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
6/23/04 09:44:48 AM
DRUG SAFETY OFFICE REVIEWER

Gerald DalPan
6/24/04 10:13:16 AM
MEDICAL OFFICER

Office of Drug Safety

Memo

To: Bob Rappaport, M.D.
Director, Division of Anesthetic, Critical Care and Addition Drug Products, HFD-170

From: Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator, Division of Medication Errors and Technical Support, HFD-420

Through: Alina Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support, HFD-420

Carol Holquist, R.Ph.
Director, Division of Medication Errors and Technical Support, HFD-420

CC: Sara Stradley
Project Manager, Division of Anesthetic, Critical Care and Addition Drug Products, HFD-170

Date: June 14, 2004

Re: ODS Consult 02- 0105-2; Palladone™ (Hydromorphone Hydrochloride Extended-Release Capsules) 12 mg, 16 mg, 24 mg, and 32 mg; NDA 21-044

This memorandum is in response to a May 24, 2004, request from your division for a final review of the proprietary name, Palladone™. The blister label, container label, carton and insert labeling were provided for review and comment.

The proposed proprietary name, Palladone™, was found acceptable by DMETS on July 2, 2002, (ODS Consult # 02-0105). The Division of Medication Errors and Technical Support (DMETS) has not identified any additional proprietary or established names that have the potential for confusion with Palladone™ since we conducted the initial review that would render the name objectionable. In addition, the Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the proposed name acceptable from a promotional perspective.

DMETS has reviewed the blister label, container label, carton and insert labeling, and has focused on safety issues relating to prevention of medication errors DMETS has identified the following areas of improvement that might minimize potential user error.

A. BLISTER FOIL LABEL (12 mg, 16 mg, 24 mg, and 32 mg)

Revise the established name to read "capsule" rather than "capsules" as there is only one capsule in each blister.

B. CONTAINER LABEL (12 mg, 16 mg, 24 mg, and 32 mg)

The font size of the area including the usual dosage and storage requirements is small and difficult to read. Please revise.

C. CARTON LABELING (Blister Box – 25 capsules, Institutional Use)

No comment.

D. INSERT LABELING

We have learned from the Division that the alternate administration instructions [redacted] will be removed from the Dosage and Administration section of the insert. Please ensure that this occurs. As of the submission dated May 17, 2004, the draft still included this information in addition to a warning against opening the capsules for any reason.

E. PATIENT PACKAGE INSERT

DMETS' comments regarding the patient package insert are incorporated in the Division of Surveillance, Research, and Communication Support's review dated June 23, 2004.

In summary, DMETS has no objection to the use of the proprietary name, Palladone™. In addition, we recommend implementation of the labeling revisions as outlined in this review. We consider this a final review. If the approval of the NDA is delayed beyond 90 days from the signature date of this document, the name with its associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document.

If you have any questions, need clarification, or would like to arrangements meeting for DMETS input, please contact the medication errors project manager, Same Beam, at (301) 827-2102.

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/s/

Tia Harper-Velazquez
6/28/04 10:09:40 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
6/28/04 10:47:34 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/28/04 02:23:04 PM
DRUG SAFETY OFFICE REVIEWER

5/25/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-044

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Richard J. Fanelli, Ph.D.
Senior Director, US Regulatory Affairs

Dear Dr. Fanelli:

We acknowledge receipt on May 18, 2004 of your May 17, 2004 resubmission to your new drug application for Palladone (hydromorphone hydrochloride extended-release capsules).

We consider this a complete, class 1 response to our September 13, 2002 action letter. Therefore, the user fee goal date is July 18, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. As stated in our "approvable" letter dated September 13, 2002, pediatric studies for this product are deferred until December 31, 2005.

If you have any question, call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara Stradley, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sara Stradley
5/25/04 03:58:06 PM

5/25/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-044

INFORMATION REQUEST LETTER

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Richard J. Fanelli, Ph.D.
Senior Director, US Regulatory Affairs

Dear Dr. Fanelli:

Please refer to your December 28, 1998 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Palladone (hydromorphone hydrochloride extended-release capsules).

We also refer to your submissions dated February 12 and May 17, 2004.

The Controlled Substance Staff (CSS) has reviewed the referenced materials and has the following comments and recommendations. We request a prompt written response in order to continue our evaluation of your NDA.

1. The limited rollout will proceed [ ], however assessment of the rollout phase [ ] The number of physicians to which Palladone will be promoted will be increased considerably at the [ ] of the rollout. So it will be difficult to evaluate the impact of this phased introduction of the product at — when changes occurred from [ ] period to the [ ] period. Could the plan be evaluated at 6 months and before a wider promotion of the product?

2. Provide a description of the standard operating procedures in place to identify inappropriate prescribing and clarification of the meaning of "inappropriate prescribing." "Appropriate prescribing" must be defined. In addition, describe how you will convey to the physician that he or she is not prescribing the product appropriately. Describe the mechanism to distribute additional educational materials to those physicians who are considered inappropriate prescribers. Describe how you will contact the State Medical Boards when a pattern of inappropriate prescribing is detected.

3. In reference to the sample of doctors who will be visited by sales representatives during the rollout phase, provide information on geographic areas (rural *vs.* urban) represented by the targeted physicians.

4. For comparative purposes, provide information on how the marketing of Palladone during the rollout compares to the way that OxyContin was launched. Describe how many physicians were detailed during the first six months of OxyContin's introduction and what specialties were targeted.

5. You state that [ ] will be set up to identify if practitioners who have not had any sales calls start prescribing Palladone. Provide description of this '[ ]

6. Provide a copy of the Palladone Capsules Prescriber Packet that will be distributed by sales representatives and content of the educational information provided to targeted physicians.

7. Describe how you will evaluate the performance of the sales force.

8. During the rollout period, describe what other marketing promotional strategies are going to be used in addition to detailing by the sales force.

9. Clarify it your advertisement plans include [ ] Describe your plans for drug advertising.

If you have any questions, call Sara E. Stradley, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Supervisory CSO
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
5/25/04 08:45:02 AM

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431
(203) 588 8000
Fax (203) 588 8850
www.purduepharma.com

May 20, 2004

Bob A. Rappaport, M.D., Director
Division of Anesthetic, Critical Care and
Addiction Drug Products
Office of Drug Evaluation 2
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-170, Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

DESK COPIES

GENERAL CORRESPONDENCE
RESPONSE TO REQUEST FOR INFORMATION

Re: Palladone™ (hydromorphone hydrochloride extended-release) Capsules
NDA #21-044

Dear Dr. Rappaport:

Reference is made to the Purdue Pharma L.P. (PPLP) New Drug Application #21-044 for Palladone™ (hydromorphone hydrochloride extended-release) Capsules submitted to the Agency on December 29, 1998, and to the amendments to this NDA dated March 30, 2001 and March 12, 2002. Reference is also made to the September 13, 2002 approvable action letter, our October 4 and November 26, 2002 responses and to our February 12, 2004 submission with plans for a limited rollout and evaluation metrics.

Reference is also made to our May 17, 2004 Resubmission which contains a complete response to the September 13, 2003 approvable letter. Per my telephone conversation on May 19, 2004 with Sara Stradley, Project Manager, included herein is a CD which contains a word version of the package insert (PI) and the patient package insert (PPI) including both the redline strike-out and the clean copy. In addition, included on this CD is a PDF version of the blister packages, bottle labels and cartons for all four bottle strengths of Palladone Capsules.

Lastly, included herein are four (4) hard copy sets of the blister packs, bottle labels and cartons for all four bottle strengths. The requested desk copies will be forwarded to the Agency under separate cover.

P:\Medical\DRAC\BethC\Palladone\resubmision\pippilabels.doc

If you have any questions, please do not hesitate to contact me at the number(s) listed below.

Sincerely,

Beth Connelly
Manager, U.S. Regulatory Affairs
Telephone: (203) 588-7289
Facsimile: (203) 588-6229

enclosure

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

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Purdue Pharma L.P.	May 20, 2004
TELEPHONE NO *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(203) 588-8000	(203) 588-6229
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
One Stamford Forum Stamford, CT 06901-3431	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-044

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
hydromorphone hydrochloride	Palladone™ (Hydromorphone Hydrochloride Extended Release) Capsules

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
4,5a - epoxy-3-hydroxyl-17-methylmorphinan-6-one-hydrochloride

CODE NAME *(If any)*
HHER

DOSAGE FORM:	STRENGTHS	ROUTE OF ADMINISTRATION
capsules (extended release)	12, 16, 24 and 32 mg	Oral

(PROPOSED) INDICATION(S) FOR USE.

[ ]

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (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 N/A 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
General Correspondence: Response to Request for Information

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.)
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☐	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)* - General Correspondence: Response to Request for Information

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
	Beth Connelly Manager, U.S. Regulatory Affairs	5/20/04

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
One Stamford Forum Stamford, CT 06901-3431	(203) 588-8365

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Department of Health and Human Services
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Rockville, MD 20852-1448

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

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20 Page(s) Withheld

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✓ § 552(b)(5) Draft Labeling

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: May 19, 2004

To: Bob A. Rappaport, M.D., Director,
Division of Anesthetic, Critical Care
and Addiction Drug Products (HFD-170)

Through: Deborah B. Leiderman, M.D., Director,
Controlled Substance Staff (HFD-009)

From: Silvia N. Calderon, Ph.D., Team Leader,
Controlled Substance Staff (HFD-009)

Subject: Consultation regarding Response to Agency Request-Limited Rollout and Evaluation Metrics, NDA 21-044, Palladone Extended Release Capsules
Sponsor: Purdue Pharma L.P.
Materials reviewed in this consult: General correspondence, February 12, 2004
Meetings with the Sponsor related to the current Submission: December 17, 2003

BACKGROUND

This memorandum responds to the Division of Anesthetic, Critical Care, and Addiction Drug Products' request for CSS consultation on the proposed Palladone rollout plan and evaluation metrics. In this submission the Sponsor presents information on their proposed rollout plan and metrics in response to the Anesthetic and Life Support Drugs Advisory Committee's (September 9-10, 2003) recommendation, a subsequent meeting with FDA on December 17, 2003 and a follow-up telecon with the Sponsor on February 12, 2004.

Regarding Palladone's RMP, CSS's prior consultations (September 26, 2001 and September 12, 2002) included several recommendations to be addressed by the Sponsor at the time of the resubmission of the NDA.

Prior RMP submissions were dated July 17, 2001; July 2, 2002; September 9, 2002, December 23, 2002, March 5, 2003, a follow up meeting with the Sponsor on June 23, 2003 and the Anesthetic and Life Support Drugs Advisory Committee's recommendation on September 9-10, 2003.

The limited introduction phase is one of the components of Palladone's Risk Management Program (RMP). Palladone's proposed RMP includes appropriate labeling, a phased launch, professional education, primary market research to monitor for appropriate patient selection and delivery of key safety messages and proactive surveillance. Primary market research includes requesting information via surveys, focus groups, and interviews.

The goals of the limited rollout are 1) to ensure appropriate and safe use of the product, 2) reduce abuse and 3) minimize diversion. To meet the objectives of the limited rollout the Sponsor proposes to detail the product by sales representatives to a reduced number of prescribers and to limit marketing. The limited rollout will focus on prescribers with known experience with single entity opioids and who are most likely to prescribe Palladone, based on their prescribing practices. The limited rollout will [ ] however assessment of the rollout phase [ ] During this period, the Sponsor will monitor and analyze promotional messages and signals of abuse. Although the Sponsor states that appropriate action will be taken if needed, there is no information on what kind of actions will be taken.

SUMMARY OF INFORMATION ON THE PROPOSED LIMITED ROLLOUT PERIOD

- Proper prescribing practices

[redacted]

- Sales Force Training and Promotion

The Sponsor states that [ ] will be set up to identify if practitioners who have not had any sales calls start prescribing Palladone. If this happens, Purdue will send a Prescriber Packet to the identified physician and the physician will receive a non-promotional follow up call.

In addition a toll free number will be included in the promotional materials for physicians to contact Purdue if they are concerned about marketing and sales practices.

- Metrics for Evaluation of Limited Rollout

Evaluation and success of the limited introduction phase will be accomplished by the following minimum metrics:

- **Minimum Metrics 1**. Determination of the number and rate of serious adverse events with particular attention to overdose and death using spontaneous reports and investigation of the reports.

  Purdue will provide a biannual report to FDA focusing on serious adverse events, particularly those related to overdose and death and will determine when possible if the case involved medical or non-medical Palladone.

- **Minimum Metrics 2**. Determination of the number and rates of misuse, abuse and diversion using an active surveillance program that includes several data sources such as DAWN, NSDUH, TESS, RADARS and outpatient drug use patterns.

  The calculation of rates will use denominators that will take into consideration potency and duration of action. The use of two denominators is being evaluated. One considers delivery units or individual units of each drug dispensed in retail pharmacies, and the other denominator will consider minimal divertible units. For minimal divertible units is to understand the number of individual units of each drug dispensed in retail pharmacies divided by the smallest available nonparenteral dosage form.

- **Minimum Metrics 3 A**. Evaluation of compliance with indicated usage of the product using drug utilization databases to identify the number and percent of prescriptions provided to patients with or without prior prescription of any opioid product.

  Purdue will provide information provided by — on a [ ] period. Purdue will capture prior opioid therapy use before starting Palladone based

on "switch" data from 14,000-20,000 retail pharmacies. This database captures data in retail pharmacies and will not include opioid use in an institutional setting.

- **Minimum Metrics 3 B.** Evaluation of number of prescriptons written by oncologists and pain specialists versus other specialties and primary care physicians.

  Purdue will use IMS Health's National Prescription Audit (NPA) to monitor prescriptions filled for Palladone by dosage strength, identified by prescriber specialty.

- **Minimum Metrics RMP**. Evaluate and measure the quality of the healthcare provider education.

  Purdue will conduct research to capture the recall of key messages, which were communicated during sales calls or visits, by health care professionals involved in the limited rollout.

COMMENTS AND RECOMMENDATIONS

1. The limited rollout will [however assessment of the rollout phase will] The number of physicians to which Palladone will be promoted will be increased considerably [ ] of the rollout. So it will be difficult to evaluate the impact of this phased introduction of the product — when changes occurred from [ ] period. Could the plan be evaluated at 6 months and before a wider promotion of the product?
2. The Sponsor should be asked to provide a description of the standard operating procedures in place to identify inappropriate prescribing and clarification of the meaning of "inappropriate prescribing." "Appropriate prescribing" must be defined. In addition, how will the Sponsor convey to the physician that he or she is not prescribing the product appropriately? Is Purdue going to distribute additional educational materials to those physicians who are considered inappropriate prescribers? Is Purdue going to contact State Medical Boards when a pattern of inappropriate prescribing is detected?
3. In reference to the sample of doctors who will be visited by sales representatives during the rollout phase, please provide information on geographic areas (rural *vs.* urban) represented by the targeted physicians.
4. For comparative purposes, please provide information on how the marketing of Palladone during the rollout compares to the way that OxyContin was launched. How many physicians were detailed during the first six months of OxyContin's introduction? What specialties were targeted?
5. The Sponsor states that [ ] will be set up to identify if practitioners who have not had any sales calls start prescribing Palladone. Please provide description of this [ ]

6. Please provide a copy of the Palladone Capsules Prescriber Packet that will be distributed by sales representatives and content of the educational information provided to targeted physicians.
7. How will the Sponsor evaluate the performance of the sales force?
8. During the rollout period, what other marketing promotional strategies are going to be used in addition to detailing by the sales force?
9. Do advertisement plans include [ ] What are the plans for drug advertising?
10. Full assessment of the proposed rollout phase will be best conducted once we have received the full RMP submission.

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/s/

Silvia Calderon
5/19/04 03:10:24 PM
CHEMIST

Deborah Leiderman
5/19/04 03:28:26 PM
MEDICAL OFFICER

Stradley, Sara

From: Calderon, Silvia N
Sent: Tuesday, April 20, 2004 3:24 PM
To: Stradley, Sara
Cc: Leiderman, Deborah
Subject: RE: Palladone PPI

Follow Up Flag: Follow up
Flag Status: Flagged

Sarah,

We didn't have comments on the PPI.

Thank you,
Silvia

-----Original Message-----
From: Stradley, Sara
Sent: Tuesday, April 20, 2004 3:17 PM
To: Calderon, Silvia N; Stradley, Sara
Subject: Palladone PPI

Silvia
Did you have any comments on the PPI? The original consult requested comments on the PI and PPI. I know the PI took a priority but wanted to know if you have any comments on the PPI. I have attached a draft of the PPI (with comments by Sharon and ODS). This is based on the Oct 8, 2002 submission in the EDR.

<< File: PPI OT00470 October 22002 Redline1 sh dsrcs.doc >>

Sara E. Stradley
Regulatory Project Manager
Division of Anesthetic, Critical Care and Addiction Drug Products (DACCADP)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
phone 301-827-7430
fax 301-443-7068

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/s/

Sara Stradley
4/21/04 11:37:21 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-044

3/3/04

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Richard J. Fanelli, PhD
Senior Director, US Regulatory Affairs

Dear Dr. Fanelli:

Please refer to the teleconference meeting between representatives of your firm and FDA on February 12, 2004. The purpose of the meeting was to follow-up the December 17, 2003 meeting in which databases that might be useful for surveillance of abuse, misuse and diversion were discussed.

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, call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

SPONSOR MEETING ATTENDEES

Meeting Date: February 12, 2004

Location: teleconference

Application: NDA 21-044

Drug: Palladone (hydromorphone HCl extended-release) capsules

Indication: Management of persistent moderate to severe pain

Sponsor: Purdue Pharma, L.P.

Type of Meeting: Guidance

Minutes Recorder: Sara Stradley, M.S., Regulatory Project Manager

Purdue Pharma	**Title**
Richard J. Fanelli, PhD	Senior Director, US Regulatory Affairs
Sydney Schnoll, MD, PhD	Executive Medical Director, Health Policy
David Haddox, DDS, MD	Vice President, Health Policy
FDA	**Title**
Bob A. Rappaport, MD	Division Director, DACCADP
D. Elizabeth McNeil, MD	Medical Reviewer, DACCADP
Rigoberta Roca, MD	Deputy Director, DACCADP
Sara Stradley, MS	Regulatory Project Manager, DACCADP
Mary E. Willy, PhD	Team Leader, Epidemiologist, DDRE
Martin Pollack, PhD	Safety Evaluator, DDRE
Gianna Rigoni, PharmD, MS	Epidemiologist, DSRCS
Gerald DalPan, MD	Division Director, DSRCS
Silvia Calderon, PhD	Pharmacologist, CSS
Deborah Leiderman, MD	Director, CSS

Meeting Objective: The purpose of the meeting was to follow-up the December 17, 2003 meeting in which databases that might be useful for surveillance of abuse, misuse, and diversion were discussed.

General Discussion: After brief introductions, the meeting focused on the questions from the January 20, 2004, meeting package.

1. *Could the Agency make recommendations on how to collect "patient-level Rx drug use longitudinal data to look for evidence of patients switching between insurance and cash payments and/or pharmacy shopping by geographic area"? All of the databases we have checked have deficiencies in collecting such data. Some cannot pick up patients who switch pharmacies — while others cannot pick up patients who switch ID cards with changes of name or birth date and only pick up about 50% of patients in a given pharmacy — and finally, the best data on cash payment is at the physician level, not the patient level (IMS).*

   The Agency stated that they cannot recommend one database over another and asked the Sponsor to clarify which databases they have used and why these were not sufficient. The Sponsor stated that most databases have a limited amount of patient level data and that patients that "shop" for a pharmacy and/or doctor may not be captured in these data. The Sponsor has looked at data on a national level and found that abuse occurs in localized regions. The Sponsor stated it was hard to obtain sufficient data.

   The Agency asked if the Sponsor has examined managed care databases. The Sponsor stated that they are currently looking at managed care databases to try to identify patterns of abuse and misuse and agree these databases would be useful if they have sufficient numbers of prescribers. The Sponsor also mentioned their collaboration with an unspecified number of managed care organizations (MCOs) to develop the Controlled Substance-Patterns of Utilization Requiring Evaluation (CS-PURE) algorithm to assist MCOs in identifying patterns of abuse and misuse among their covered lives. The Sponsor stated that each MCO uses a different algorithm, but they are examining the possibility of utilizing such a database. The Sponsor also expressed their concerns with not being able to obtain the needed data because of current Health Insurance Portability and Accountability Act (HIPAA) regulations. The Agency encouraged the Sponsor to assess use patterns as well as abuse patterns in their various data sources.

   The Agency suggested that the Sponsor examine drug use databases as possible signal generators. There are no validated algorithms for identifying abuse and/or misuse in drug use databases at this time, but the Agency suggested that the Sponsor examine the number of pharmacies each patient frequents, the number of prescribers seen by each patient, and other medications in the patient's profile as possible proxies. The Sponsor

stated that it is difficult to trace a patient when they switch pharmacies since many databases would show them as a different person. The Sponsor also stated that abusers will switch pharmacies and their identification, making it hard to track them. The Agency stated that this may be the case with experienced addicts, but this method may assist in identifying legitimate users that develop an iatrogenic addiction. The Sponsor agreed to this suggestion but was not sure how to find this type of information. The Agency advised the Sponsor to examine their managed care databases and utilize their current algorithms to attempt to obtain this information.

The Agency requested that the Sponsor provide information on methods used to this point with the managed care databases. The Sponsor agreed to provide this information.

2. *Why is the Agency only interested in single entity Schedule II products as comparators? Combination products are very widely abused.*

The Agency stated that Schedule II and III products are regulated differently. Hydrocodone is extensively abused and prescribing patterns differ from Schedule II products. The Agency would like the Sponsor to compare Palladone rates of use, abuse, and misuse to other Schedule II single-entity products and encourages the Sponsor to conduct separate analyses to compare Palladone rates of use, abuse, and misuse to combination and Schedule III products of interest.

The Sponsor stated that they are working on a publication with regards to the appropriate denominator. The Sponsor stated that they have narrowed it down to two denominators and will provide information on these to the Agency. Briefly, the two denominators the Sponsor is examining are the number of units (i.e., tablets, capsules, transdermal systems, etc.) dispensed ("load of product") by three-digit zip code and the minimal divertable unit (i.e., smallest available dose of product that can be prescribed - i.e., hydromorphone 8mg = 4 divertable units based on 2mg dose). The Sponsor stated that these methods were used by DEA to identify areas of diversion.

The Agency requested further information on these denominators be submitted. The Sponsor encouraged the Agency to attend the RADARS meetings for this information.

3. *Many potency calculations have been done with parenteral products with little information about transdermal products. Does the Agency have any recommendations on how to deal with this? Much of the abuse of transdermal products is from used patches. How should this be calculated into potency considerations?*

The Division stated that there are standards used in clinical settings that address the issue of potency.

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/s/

Sara Stradley
3/3/04 10:36:35 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-044

1/16/04

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Richard J. Fanelli, Ph.D.
Director, US Regulatory Affairs

Dear Dr. Fanelli:

Please refer to the meeting between representatives of your firm and FDA on December 17, 2003. The purpose of the meeting was to discuss the outcomes of the September 9-10, 2003 advisory committee meeting.

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, call me at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Sara E. Stradley
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Industry Meeting Minutes

Meeting Date: December 17, 2003

Location: Parklawn Building, Conference Room C

NDA/ Name: NDA 21-044

Sponsor: Purdue Pharma

Type of Meeting: Guidance

Meeting Chair: Steve Galson, MD, Acting Director, CDER

Minutes Recorder: Sara Stradley, MS, Regulatory Project Manager

Purdue Pharma	Title
Richard J. Fanelli, PhD	Director, US Regulatory Affairs
Paul Goldenheim, MD	Executive Vice President, Worldwide R&D & CSO
J. David Haddox, DDS, MD,	Vice President, Health Policy
Ellen Ingber	Executive Director, Project Management
Michael Innaurato	Group Executive Director, Marketing
Robert Reder, MD	Vice President, Medical Affairs & Worldwide Drug Safety
Anthony Santopolo, MD,	Vice President, US Regulatory Affairs
Sidney Schnoll, MD, PhD	Executive Medical Director, Health Policy
FDA	**Title**
Bob Meyer, MD	Director, OND II
Bob A. Rappaport, MD	Division Director, DACCADP
Mark Goldberger, MD	Acting Deputy Director, CDER
Steve Galson, MD	Acting Director, CDER
Terry Martin	Regulatory Health Project Manager, OEP
Sharon Hertz, MD	Team Leader, Analgesics, DACCADP
Celia Winchell, MD	Team Leader, Addiction Drug Products Acting Deputy Director, DACCADP
Anne Trontell, MD, MPH	Deputy Office Director, ODS
Mary E Willy, PhD	Team Leader, Epidemiologist, DDRE
Lanh Green, PharmD, MPH	Team Leader, Safety Evaluator, DDRE
Sandy Birdsong	Regulatory Project Manager, DDRE
Martin Pollack, PhD	Safety Evaluator, DDRE
Gerald DalPan, MD	Director, DSRCS
Gianna Rigoni, PharmD, MS	Epidemiologist, DSRCS
D. Elizabeth McNeil, MD	Medical Reviewer

Mwango Kashoki, MD	Medical Reviewer
Deborah Leiderman, MD	Director, CSS
Silvia Calderon, PhD	Pharmacologist, CSS
Sara Stradley, MS	Regulatory Project Manager, DACCADP

Meeting Objective(s): The purpose of this meeting was to discuss the outcomes of the advisory committee meeting held on September 9-10, 2003.

General Discussion: After introductions, the meeting focused on the risk management plan for Palladone. The slides presented are in italics and any discussion follows.

Introduction

Dr. Galson stated that this meeting is to provide the firm with the Agency's expectation for the Palladone risk management activities. In light of the OxyContin experience, the known abuse potential of hydromorphone, and the high potency of this product, the Agency feels that a comprehensive risk management strategy is critical to assure that this drug is properly prescribed, properly used and does not become a problem in terms of abuse, misuse and overdose.

Dr. Galson stated that the Agency has had extensive internal discussions on risk management activities for potent opiates following the ALSDAC meeting this Fall. The Agency received the strong message from the Committee that in addition to careful labeling and risk management activities for Palladone, a limited roll-out, first proposed by Purdue Pharma, was strongly endorsed, though for a more extended period of time and with more extensive measurement of the success of particular elements of the Risk Management Plan (RMP). These metrics should be assessed prior to broadening the marketing efforts.

CDER strongly believes that Palladone should have a solid RMP in place prior to marketing and that the initial marketing and detailing should be restricted to oncologists and pain specialists. This limited detailing and marketing effort should be in effect for at least 12 months, following which we would expect an assessment of key outcomes from the RMP and marketing – particularly focusing on appropriate prescribing (compliance with indicated usage), abuse, diversion, misuse, overdose, and other serious adverse outcomes. We would expect discussions with you on these data and incorporation of any necessary changes to the RMP prior to expanding the marketing of the product to a more general physician base.

Dr. Galson stated that the Agency's staff from OND, CSS and ODS would discuss the elements of the RMP that we consider important, some of the metrics the Agency would propose as possible assessments of the effects of the RMP, and other related concerns and topics.

The Sponsor stated that they have similar views and the same objective as the Agency. The Sponsor wants to assure the safe use of Palladone and minimize abuse and diversion with efforts which would include: an appropriate label, phased launch, significant professional educational component to risk management plans, appropriate safety message, and proactive surveillance program.

The Sponsor also stated that they would like to propose enhanced language in the labeling which would include sections from the risk management plan. (Note: A submission was sent to the Agency dated December 10, 2003, but was not reviewed for this meeting).

The Sponsor is also looking at new technology to prevent diversion [redacted] The Sponsor stated that, in the future, it may be possible to follow every bottle through the supply chain.

General Comments on the Package Insert (PI) and Risk Management Plan (RMP)

Palladone PI and RMP Educational Components

- *The PI has undergone review by the Division. Language added pertaining to risk of misuse and addiction and safety concerns will be described.*

- *The RMP has been reviewed. Areas for additional emphasis in the educational materials will be described.*

Package Insert

Additional role of prescribers:

- *Screen for risk of abuse*
  - *Personal or family history of abuse*
  - *Certain psychiatric diseases*
- *Monitor for signs of abuse, misuse, addiction*

Patient selection

- *Greater emphasis on assessing adequacy of IR formulations before switch to MR*

Safety considerations

- *Warning of risk from overestimation of first dose*
- [redacted]

RMP Educational Material

- *Additional emphasis needed for use of:*
  - *Physician/patient contracts*
  - *Screening for greater risk of abuse based on personal or family history*
  - *Monitoring for signs or symptoms of iatrogenic addiction, abuse, misuse, or diversion*

Discussion

The Agency stated that the PI has undergone internal review and revision and the revised label would be sent to the Sponsor. The revised label will include recommendations that prescribers screen for risk of abuse (i.e., personal or family history of abuse, and certain psychiatric diseases) and monitor for signs of abuse, misuse, and addiction. The Agency stated that language has been added providing greater emphasis on assessing adequacy of immediate-release (IR) formulations before switching to a modified-release (MR) product. The Agency also revised several safety considerations in the label (i.e, warning of risk from overestimation of first dose [ ]

The Sponsor expressed concern about [ ] directions from the package insert. The Sponsor stated that [ ] advantageous to extremely ill patients. The Sponsor stated that they will provide alternative approaches for dosing in this setting.

Comments on the Palladone Rollout

Metrics for Evaluation of Palladone Rollout

Purdue's Palladone RMP Objectives

- *Ensure proper use*
  - *Through proper patient selection and prescribing & prevention of unintentional exposure*
- *Reduce abuse*
  - *Through community-based interventions & healthcare professional education*
- *Minimize diversion*
  - *Through law enforcement support, supply chain integrity, & healthcare professional education*

FDA Recommedations

- *Sponsor should design and use multiple metrics to evaluate risk management*
  - *Limited introduction phase (rollout)*
  - *Fully implemented phase*
- *Metrics data on rollout should cover the 12 months after product launch*
  - *Report with analyses and data should be available for independent FDA analyses within 3-4 months of dataset closure*

Minimum Candidate Rollout Metrics - 1

- *Determine the number/rate of serious adverse events (particularly overdose and death)*
  - *Provide rates of these events using, at a minimum, spontaneous reports*
  - *Investigate reports of serious adverse events to determine the nature of patient use (medical or nonmedical)*

Minimum Candidate Rollout Metrics – 2

- *Determine the rates of misuse/abuse (and their consequences such as death) and diversion using an active surveillance program that includes a variety of data sources from different populations, such as:*
    - *DAWN*
    - *National Survey on Drug Use and Health*
    - *Toxic Exposure Surveillance System (TESS)*
    - *RADARS*
    - *Outpatient drug use patterns*
        - *Using sales and prescriptions to monitor for disproportionate increases by geographic area*
        - *Explore the use of patient-level, Rx drug use longitudinal data to look for evidence of patients switching between insurance and cash payments and/or doctor/pharmacy shopping, by geographic area*

Minimum Candidate Rollout Metrics – 3

- *Evaluate compliance with indicated usage via drug utilization databases to identify the number and percent of Palladone prescriptions provided to patients with/without prior prescription of any opioid product*
    1. *Examine with longitudinal, patient level data the extent of antecedent use of specific individual opioid products, particularly immediate-release hydromorphone, prior to Palladone*
    2. *Examine percent of Palladone prescriptions written by oncologists and pain specialists versus other specialties and primary care providers*

Candidate RMP Metrics - 1

- *Descriptive analysis of community interventions*
    - *Provide number of*
        - *intervention programs*
        - *enrollees in each program*
        - *sites*
    - *Description of each intervention activity*
    - *Description of the population participating*

Candidate RMP Metrics – 2

- *Measure the quality of the healthcare provider education*
    - *The type and number of methods used*
    - *The number of physicians enrolled or participating*
    - *The results of testing physician knowledge on prevention of/intervention for abuse*
    - *The numbers and types of phone calls to toll free number*

Candidate RMP Metrics – 3

- *Evaluate patient provider agreement usage*
    - *Provide the number of signed agreements relative to the number of Palladone prescriptions and/or patients*
        - *By geographic areas*
        - *By physician specialty*

Candidate RMP Metrics - 4

- *Assess the extent of patient education*
    - *Provide survey information about patient's counseling experience prior to receiving their first prescription and their knowledge of the drug's addiction potential*
    - *Enumerate the numbers and types of phone calls to the toll free number proposed for patients*

Candidate RMP Metrics - 5

- *Evaluate the type of detailing provided*
    - *Provide summary information on the type, content, and number of journal advertisements*

Comparators for analyses

- *Morphine, oxycodone, hydromorphone and fentanyl*
    - *Stratified by long and short acting*
    - *Adjusted for potency*
    - *Only Schedule II controlled substances*
    - *No combination products*

Conclusions

1. *Metrics data must be made available to FDA*
    a. *Deaths and overdoses when used appropriately*
    b. *Deaths and overdoses when misused/abused/diverted*
    c. *Other instances of misuse/abuse/diversion*
    d. *Compliance with indicated use in patients*
2. *All data sources have limitations so*
    a. *Variety of populations helpful*
    b. *Sponsor should consider providing comparisons of rates using different denominators (same numerators)*
3. *Future submissions need to provide details of any interventions and outcomes*

DISCUSSIONS

The Sponsor stated that they could collect metrics data that reflect the top four items listed in the conclusions slide. These would include deaths and overdoses when used appropriately, deaths and overdoses when misused/abused/diverted, other instances of misuse/abuse/diversion, and compliance with indicated use in patients. The Agency stated that the Sponsor should evaluate the metrics and propose a detailed plan to the Agency. The Sponsor agreed to do so.

The Agency stated that data on specific Palladone cases or, if not noted, hydromorphone cases, should be collected and the Agency recommended that these data be compared to similar data on other single entity opioid drug products, specifically excluding combination opioid products.

The Sponsor asked for clarification on the recommendation to have the comparator analysis including only Schedule II drugs. The Agency stated that the level of control under the Controlled Substances Act is similar and it is, therefore, a more appropriate comparison.

The Sponsor asked if other companies would be held to the same standards. The Agency stated that we would certainly expect similar products will have similar risk management plans, though particulars may vary according to the specifics of each product.

The Sponsor expressed concern that focusing on the percent of Palladone prescriptions written by oncologists and pain specialists versus other specialties and primary care providers might not reflect market reality. The Sponsor stated that many physicians work in the pain setting but may not be referred to as pain specialists.

The Sponsor stated that the 12 month initial launch, plus the 3-4 month data analysis would be acceptable. The Sponsor presented a brief overview of their plan.

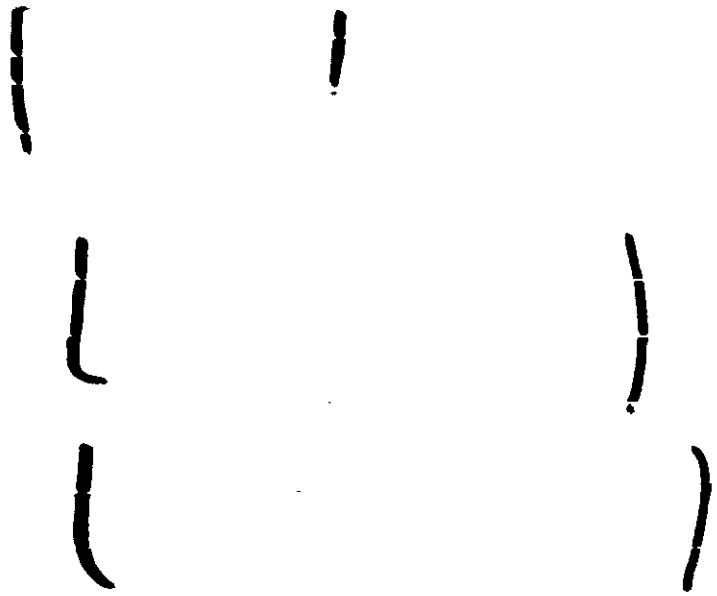
Purdue's Slides

Palladone Capsules
Objectives

- *Ensure appropriate and safe use of Palladone*
- *Minimize abuse and diversion*

Comprehensive RMP including but not limited to:

- *Appropriate product labeling*
- *Phased launch*
- *Professional education*
- *Primary market research with prescribers to ensure:*
  - *appropriate patient selection*
  - *delivery of key safety messages*
- *Proactive surveillance*



The Agency requested additional details on the Sponsor's plan. The Sponsor stated that the — system is based on marketing and sales practices and will target high prescribers of single entity opioids. The Agency believes that although this plan may select the practitioners most familiar with the prescribing of these products, there is a concern that high volume physicians may also include those who are inappropriately prescribing these products . The effect of including inappropriately prescribing physicians during the initial rollout could result in difficulty interpreting the data.

The Agency also questioned how the limiting of target physicians at rollout would affec — The Sponsor stated that they have not worked out the details yet, but that they planned only to [ ] targeting allowed physician specialties at each stage of the rollout.

The Sponsor stated that the rollout period would be limited to prescribers of single entity opioids (SEO) and not combination products. The Agency requested more details on how the deciles provided by the Sponsor were derived. The Sponsor agreed to provide these details.

The Sponsor stated that they do want to include primary care physicians, but not in the first part of the rollout. The Agency requested that the Sponsor submit an accurate timeline for this rollout, including details on when specific groups of physicians will be targeted. The Sponsor agreed to provide this timeline.

The Sponsor stated that they will provide an update on the participating Poison Control Centers that provide data collected to RADARS.

The Agency and the Sponsor agreed that future meetings would be needed to review and evaluate the phased launch rollout and other aspects of the risk management plan.

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/s/

Sara Stradley
1/16/04 08:52:36 AM

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 13, 2003

TO: Bob A. Rappaport, M.D., Acting Director
Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170

FROM: Office of Drug Safety
Division of Surveillance, Research and Communications Support (DSRCS), HFD-410
Division of Medication Errors and Technical Support (DMETS), HFD-420
Division of Drug Risk Evaluation (DDRE), HFD-430

SUBJECT: Consult: Review of Revised Palladone/Extended-Release Hydromorphone Risk Management Plan Dated March 5, 2003
PID#: D030156

I. EXECUTIVE SUMMARY

As requested from the Division of Anesthetic, Critical Care, and Addiction Drug Products, the Office of Drug Safety (ODS) reviewed the most recent revised risk management plan (RMP) for Palladone dated March 5, 2003, from Purdue Pharma L.P. (PPLP). The three Divisions (DSRCS, DMETS, DDRE) in ODS reviewed the RMP and provide comments on the labeling, patient education, and surveillance/intervention section of the plan. The patient package insert has been reviewed in a separate document (1).

In addition to the issues raised by the reviews of the surveillance plans for the previous Palladone RMP and the almost identical OxyContin RMP, this memorandum on the Palladone RMP recommends that comprehensive materials for the professional and patient education programs be submitted, safety issues relating to possible medication errors, and that the language in the submitted materials be consistent and at written in a simple language. Detailed descriptions should be provided on the rationale behind the selection of the databases, the strengths and limitations of these data sources, what will be done to combat those limitations, the case definitions (abuse, addiction, misuse, diversion, overdose, and inadvertent pediatric exposure; hereafter referred to as 'improper drug use'), the specific analyses that will be run, the methodology used (behind the numerator, denominator and rate calculations), the frequency of analyses, how the various data sources will be used and integrated, the types of interventions, the methods to be used to evaluate the success of the signal detection and intervention, the reporting to PPLP and FDA and the personnel involved in carrying out the processes. The signal detection definition should be expanded to address the variability in improper drug use situations including trends in improper drug use over time, the evaluation process should encompass this variability,

and the definition of an acceptable reduction in improper drug use should be stated. A list of many of the identified concerns was communicated to PPLP in a letter regarding OxyContin dated April 28, 2003 (2) and is attached at the end of the memorandum by the Division of Drug Risk Evaluation (DDRE) and the Division of Surveillance, Research and Communications Support (DSRCS), both within ODS.

[

J

III. LABELING (Section 3 of the RMP submission)

Medication Error Prevention (Package Insert and Patient Package Insert):

[

]

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_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Mark Avigan, M.D., Acting Director
Division of Drug Risk Evaluation, HFD-430
Office of Drug Safety

Toni Piazza-Hepp, Pharm.D., Acting Director
Division of Surveillance, Research, and
Communication Support, HFD-410
Office of Drug Safety

Jerry Phillips, R.P.H., Acting Director
Division of Medication Errors and
Technical Support, HFD-420
Office of Drug Safety

ODS Review Team:

Carolyn McCloskey, M.D., M.P.H., Epi, DDRE
Mary Willy, PhD, Epi Team Leader, DDRE
Gianna Rigoni, Pharm.D., M.S., Epi, DSRCS
Judy Staffa, PhD, Lead Epi, DSRCS
Jennifer Fan, Pharm.D., Safety Evaluator, DMETS
Denise Toyer, Pharm.D., SE Team Leader, DMETS

CC:

NDA 21-044	Palladone/extended-release hydromorphone
HFD-170	Hertz/Shepherd/Stradley(PM)
HFD-400	Seligman/Raczkowski/Trontell/Dempsey(PM)
HFD-430	Avigan/Willy/McCloskey/Green/Pollock/Guinn(PM)/Birdsong(PM)/Nguyen(PM)
HFD-420	Phillips/Holquist/Dallas/Toyer/Beam(PM)
HFD-410	Piazza-Hepp/Staffa/Rigoni/Best/Stephens(PM)
HFD-009	Leiderman/Calderon/Moody (PM)

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/s/

Patrick Guinn
6/13/03 02:56:03 PM
CSO
Entered in DFS for ODS Review Team

Mark Avigan
6/13/03 03:08:57 PM
MEDICAL OFFICER

Toni Piazza Hepp
6/13/03 03:49:20 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/20/03 11:06:41 AM
PHARMACIST

6/4/03

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-044

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Richard J. Fanelli, Ph.D.
Director, U.S. Regulatory Affairs

Dear Dr. Fanelli:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Palladone (hydromorphone hydrochloride extended-release) Capsules.

We also refer to your October 4, 2002, submission containing responses to all of the items identified in the September 13, 2002, approvable action letter with the exception of the issues about the product manufacturing site and the drug specifications that will be addressed under separate cover.

We have reviewed the referenced material and have the following preclinical pharmacology comments and recommendations.

1. Your proposal to submit qualification studies for the morphinone impurity (Ames bacterial reverse mutation assay and a chromosomal aberrations assay in CHO cells) as a post-approval commitment, if this is the only outstanding issue at the time of product approval, is acceptable.

2. Due to a recent evaluation of requirements to support a 505(b)(2) NDA submission by the Office of New Drugs, carcinogenicity studies are no longer a requirement for this NDA. The Agency notes that you have previously committed to perform carcinogenicity studies in rats and mice as a Phase 4 commitment and have provided a timeline in which the studies will be conducted and submitted. You are encouraged to conduct these studies in the interest of public health and should at the least conduct a review of the published literature and include any relevant information in the product label.

If you have any questions, call Sara E. Stradley, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Acting Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Bob Rappaport
6/4/03 04:41:37 PM

MEMORANDUM

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

DATE: May 19, 2003

TO: Bob Rappaport, M.D., Acting Director
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

VIA: Sara E. Stradley, Regulatory Health Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

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: Toni Piazza-Hepp, Pharm. D., Acting Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for Palladone™
(hydromorphone HCl extended-release) Capsules, NDA 21-044.

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for Palladone™ (hydromorphone HCl extended-release) Capsules, NDA 21-044. 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), 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.

Comments on the sponsor's Risk Management Plan, submitted March 12, 2003, will come separately, in an ODS combined document.

Please let us know if you have any questions. 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.

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_____ § 552(b)(5) Draft Labeling

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/s/

Jeanine Best
5/19/03 07:29:44 AM
CSO

Toni Piazza Hepp
5/19/03 02:29:42 PM
DRUG SAFETY OFFICE REVIEWER

2/7/03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-044

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Richard J. Fanelli, Ph.D.
Director, U.S. Regulatory Affairs

Dear Dr. Fanelli:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Palladone (hydromorphine hydrochloride extended-release) Capsules.

We also refer to your December 19, 2002 submission, requesting feedback on policy issues.

We have reviewed the referenced material and have the following comments and recommendations in response to your recent submission regarding a correspondence that you received from the Drug Enforcement Agency (DEA):

> First, let me make it perfectly clear that there has been no shift in FDA's regulatory policy regarding approval of controlled substances. FDA continues to make all approval decisions, including determination of the indications, as we are authorized to do under the Federal Food, Drug and Cosmetic Act. However, in the interest of protecting the public health, the Agency does take into consideration the DEA's and other federal agencies' views on how drugs such as Palladone may be most safely marketed to ensure availability of these products to patients who need them while minimizing diversion and abuse.
>
> The DEA's concerns regarding Palladone stem from their continuing experience with drugs such as oxycodone, coupled with past and present experiences with the abuse of hydromorphone. While all opiate drug products are carefully evaluated for abuse potential prior to approval, some products raise specific concerns due to a potential for increased levels of abuse and to an even greater risk for morbidity and mortality associated with diversion and abuse. Any products that raise these concerns would be most carefully reviewed by the Agency.
>
> Once again, let me emphasize that there has been no change in regulatory policy regarding the approval process for controlled substances. We have, however, brought

this matter to the attention of the Center for Drug Evaluation and Research senior management. FDA's Office of the Chief Counsel is also aware of this matter. They have been thoroughly briefed on all aspects of the Palladone application, and they continue to be actively involved in the area of risk management for opiate analgesic drug products.

I believe that this letter has addressed your questions and concerns and that a meeting is not necessary at this time. If you would still like to meet with us to discuss these issues further, please submit a meeting request to your application.

If you have any questions, call Sara E. Stradley, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Acting Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Celia Winchell
2/7/03 10:40:49 AM
for Bob A. Rappaport, M.D., Acting Division Director

MEMORANDUM

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

DATE: September 20, 2002

TO: NDA 21-044 File

FROM: Lisa Malandro, Regulatory Project Manager

SUBJECT: **Teleconference with Purdue Pharma L.P. on September 13, 2002**
NDA 21-044, Palladone (hydromorphone hydrochloride extended-release) Capsules

1. Dr. Koble presented the following question regarding packaging and labeling of the containers to the Sponsor. "In the blister packs, is differentiation between strengths indicated by color-coding like the bottles are?" The Sponsor is looking into this. Dr. Koble also indicated that the labeling for the 32 mg dose is problematic (i.e. "mg" falls outside of the box).

2. The following items will be addressed by the Sponsor following receipt of the revised package insert from the Division.

   a. [redacted] – in response to the Division's concerns that this term is misleading, the Sponsor will attempt to define it throughout the document

   b. In the "Drug Abuse and Addiction" section, the Sponsor agreed to revise the wording to clarify that the higher dose will make abuse more likely

   c. The Division agreed that use of the word [redacted] will be accepted until a Guidance document or new data are available.

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/s/

Lisa Malandro
9/30/02 12:04:14 PM
CSO

9/13/02

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-044

Purdue Pharma L.P.
Attention: Richard J. Fanelli, Ph.D.
Director
One Stamford Forum

Stamford, CT 06901-3431

Dear Dr. Fanelli:

Please refer to your new drug application (NDA) for Palladone (hydromorphone hydrochloride) Extended release Capsules.

We also refer to your submission dated July 2, 2002.

As discussed in the telephone conversation on September 13, 2002, between you and Cynthia McCormick, M.D. Director of this Division, we are enclosing the revised Risk Management plan for Palladone.

If you have any questions, call Sara Shepherd, Regulatory Project Manager, at (301) 827-7410.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthetics, Critical care, and
Addiction Drug Products
Office of Drug Evaluation ODE II
Center for Drug Evaluation and Research

Enclosure

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/s/

Parinda Jani
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✓ § 552(b)(5) Draft Labeling

MEMORANDUM

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

DATE: September 12, 2002

TO: Cynthia McCormick, M.D., Director
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

VIA: Sara E. Shepherd, Regulatory Health Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Regulatory Health Project Manager
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Anne Trontell, M.D., M.P.H., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for Palladone™
(hydromorphone HCl extended-release) Capsules, NDA 21-044.

The patient labeling which follows represents the revised risk communication materials for Palladone™ (hydromorphone HCl extended-release) Capsules. The revisions reflect changes in format, wording, and organization that are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. Comments are bolded, italicized, and underlined.

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/s/

Jeanine Best
9/12/02 01:08:40 PM
CSO

Anne, This needs to be signed-off today.

Anne Trontell
9/12/02 02:30:01 PM
MEDICAL OFFICER

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 12, 2002

To: Cynthia G. McCormick, M.D., Director
Division of Anesthetic, Critical Care
And Addiction Drug Products (HFD-170)

Through: Deborah B. Leiderman, M.D., Director
Controlled Substance Staff (HFD-009)

From: Silvia N. Calderon, Ph.D., Interdisciplinary Scientist
Ann-Kathryn Maust, M.D., Medical Officer
Controlled Substance Staff (HFD-009)

Subject: Consultation regarding proposed Risk Management Program
NDA 21-044, Palladone Extended Release Capsules
Sponsor: Purdue Pharma L.P.
Submitted to FDA July 02, 2002; Consultation date July 12, 2002

BACKGROUND

This memorandum responds to the Division of Anesthetic, Critical Care, and Addiction Drug Products's request for CSS advice and perspective on the proposed Palladone Risk Management Program (RMP) and label. Comments regarding the label and PPI have been communicated in meetings held on September 03, September 06 and September 10 and in writing on September 11, 2002. In addition, our consultation of September 26, 2001 (DFS, NDA 21-044) included several recommendations to be addressed by the Sponsor at the time of the resubmission of the NDA. This consultation reiterates and expands upon the concerns and recommendations conveyed in the September 2001 consultation.

I. Palladone Relative Potency

OxyContin and Palladone products share some similar properties but also exhibit some striking differences with respect to safety profile and abuse risks. Both products are highly concentrated, sustained release formulations of approved immediate release mu opioid analgesics. It is important to examine the relative analgesic and subjective/ psychic effect potencies of these mu opioid drugs. At equianalgesic doses, oral hydromorphone is approximately four times more potent than oral oxycodone and morphine. (See **Tables 1** and **2** below).

Therefore, the lowest dose (12-mg capsule) of Palladone is equivalent in analgesic effect to 48 mg of oral oxycodone and to 48 mg oral morphine. The highest Palladone dose (32 mg capsule) is equivalent in analgesic effect to approximately 130 mg of oral oxycodone or morphine. Hydromorphone administered parenterally is 6-7 times as potent as intravenously administered morphine when equianalgesic effects are compared. Thus injection of 32 mg Palladone is equivalent in analgesic effect to approximately 214 mg of parenteral morphine. However, when the psychic and subjective effects of oral or intravenous hydromorphone are compared to those of oral or intravenous morphine, hydromorphone is ten times as potent as morphine (Jasinski *et al.*, 1977; Hill and Zacny, 2000). Thus, 12 mg of Palladone produces psychic effects equipotent to 120 mg of morphine while 32 mg is equipotent to 320 mg of morphine.

Table 1: Relative Analgesic Potencies of Opiate Drugs

Drug	Approximate **equianalgesic** dose	
	Oral	Parenteral
MORPHINE	30 mg q 3-4 hr (around-the-clock dosing)	10 mg
HYDROMORPHONE	7.5 mg q 3-4 hr	1.5 mg
HYDROCODONE	30 mg q 3-4 hr	
METHADONE	20 mg q 6-8 hr	
OXYCODONE	30 mg q 3-4 hr	
FENTANYL		0.1 mg

Table 2: Relative Analgesic Potencies of Opiate Products

Palladone Capsules	**morphine**		**methadone**	**oxycodone**
	oral	parenteral		
12 mg	48 mg	16 mg	32 mg	48 mg
16 mg	64 mg	21mg	43 mg	64 mg
24 mg	96 mg	32 mg	65 mg	96 mg
32 mg	128 mg	43 mg	86 mg	128 mg

When comparing currently available strengths of OxyContin tablets to hydromorphone and morphine, a 40 mg OxyContin Tablet is approximately equivalent to 10 mg of hydromorphone, 40 mg of oral morphine and 27 mg of methadone (**Table 3**)

Table 3: Relative Potencies of OxyContin Tablets and other Opioid Products

OxyContin Tablets	hydromorphone	morphine		methadone
		oral	parenteral	
40 mg	10 mg	40 mg	13 mg	27 mg
80 mg	20 mg	80 mg	27 mg	54 mg
160 mg	40 mg	160 mg	53 mg	108 mg

II. ABUSE OF HYDROMORPHONE

The high dose and potency of the Palladone capsules are of concern because recent experience with abuse and misuse of OxyContin has demonstrated that the extended release property of the product is readily altered, effectively delivering a very high, potentially fatal dose of opioid drug.

Hydromorphone has a well-documented history of abuse dating back to the 1970's when hydromorphone was the drug of choice among opiate abusers who often administered the drug intravenously after crushing and dissolving the 4-mg immediate release (Dilaudid) tablets (reported to have a street value of up to $ 50 per tablet). Dilaudid continues to be commonly diverted and abused. DEA field reports describe the 4 mg tablet's street price as ranging from $40 to $65. The less common 8 mg tablet's street price has been reported to be as high as $100. In 1995, the DEA Drug Operations Section (DOS) initiated a special investigation focusing on hydromorphone. The DOS reports 878 thefts involving 458,000 dosage units of Dilaudid/hydromorphone between January 1, 2000 and September 06, 2002 (DEA data, personal communication, 2002).

Data from the Drug Abuse Warning Network (DAWN) maintained by Substance Abuse and Mental Health Services Administration (SAMHSA) provides useful comparative information regarding prescription and illicit opiate abuse rates. Prescription data from IMS (National Prescription Audit Plus) are displayed in **Table 4** to provide a context and crude denominators for the interpretation of DAWN abuse data displayed in **Table 5**.

Table 4. Drug Utilization Values Reported as Annual Prescriptions Dispensed in the U.S.A. (In Thousands) For Hydromorphone, Fentanyl and, Codeine, Hydrocodone and Oxycodone (1997-2001).

DRUGS	PROJECTED TOTAL PRESCRIPTIONS [a]				
	1997	1998	1999	2000	2001
HYDROMORPHONE					
FENTANYL					
CODEINE					
HYDROCODONE					
OXYCODONE					

[a] Source: IMS HEALTH, ™ National Prescription Audit *Plus*. Not for use outside FDA without prior clearance by IMS America.

Table 5: Estimated DAWN Emergency Department (ED) Mentions (Source: Office of Applied Studies, SAMHSA) Relative to Projected Total Number of Prescriptions Dispensed in the U.S.A. (Numbers presented in **Table 4**, Source: IMS HEALTH, National Prescription Audit *Plus*) for Hydromorphone, Fentanyl, Codeine, Hydrocodone, and Oxycodone for 1997 to 2000

DRUG	MEASURE	1997	1998	1999	2000
HYDROMORPHONE	DAWN ED Mentions (Weighted)				
	No. ED/ per Ten Thousand Dispensed Prescriptions				
FENTANYL	DAWN ED Mentions (Weighted)				
	No. ED/ per Ten Thousand Dispensed Prescriptions				
CODEINE	DAWN ED Mentions (Weighted)				
	No. ED/ per Ten Thousand Dispensed Prescriptions				
HYDROCODONE	DAWN ED Mentions (Weighted)				
	No. ED/ per Ten Thousand Dispensed Prescriptions				
OXYCODONE	DAWN ED Mentions (Weighted)				
	No. ED/ per Ten Thousand Dispensed Prescriptions				

Table 6: DAWN Medical Examiner (ME) Mentions Relative to Availability (IMS HEALTH, National Prescription Audit *Plus*) for Hydromorphone and Hydrocodone Drugs (1997-2000).

DRUG	TOTAL MEs 1997-2000	IMS, NPA*Plus*™ No. Rx (000) 1997-2000	DEATHS (DAWN ME's) RELATIVE TO TOTAL NUMBER OF PRESCRIPTIONS (IMS, NPA*Plus*™)[a] 1997-2000
HYDROMORPHONE	[redacted] *	[redacted]	[redacted]
HYDROCODONE	[redacted] *	[redacted]	[redacted]

[a]. The above ratios may be considered "crude" estimates because ME reports are not national estimates whereas the sales data represent the whole U.S. market. Until better analytical tools become available, these ratios are used for ranking purposes and were similarly calculated for hydromorphone and hydrocodone.
* Total mentions for drugs in combination and taken alone.

Although DAWN reports fewer hydromorphone ED abuse-related episodes compared to the number reported for oxycodone, hydrocodone, codeine and fentanyl, the prescription-adjusted rate of abuse for hydromorphone is dramatically higher than the other CII opiates. It is noteworthy that "Dependence" is the motive in the majority of the hydromorphone reports in contrast to the other opiates for which "Suicide" is the most frequently reported motive. DAWN data indicate that the rate of abuse of hydromorphone in 1999 and 2000 was ten to twenty times the rate of abuse of the more commonly prescribed oxycodone.

Furthermore, national survey data indicate that the abuse and misuse of prescription opiates as a class is rising. The National Household Survey for the period 1998-2001 (SAMHSA, OAS, DHHS) shows annual increases in self-reported abuse of prescription opioid analgesics. In 1998, approximately 5.3% of the surveyed population reported lifetime use while less than 1% reported use in the last month. In 2001, 9.8% reported life-time abuse while 1.6 % reported last month use. (Appropriate medical use with a physician's prescription is excluded).

The highest immediate release hydromorphone dose currently available is the 8 mg Dilaudid tablet. We anticipate that the availability of higher doses of hydromorphone (Palladone) will result in an increase in abuse, misuse, and associated deaths.

III. CONCLUSIONS AND RECOMMENDATIONS ON THE RISK MANAGEMENT PROGRAM (RMP) TO BE CONVEYED TO THE SPONSOR

The sponsor's proposed risk management program addresses three areas of concern: 1) risks posed by abuse or diversion of Palladone capsules, 2) risks posed by improper patient selection and 3) risks posed by accidental pediatric exposure.

The primary tools of the sponsor's risk management program are: appropriate labeling and promotion, professional educational programs, monitoring for misuse, abuse, addiction, diversion and overdose, and appropriate interventions when abuse or risk of abuse has been identified. The proposed Palladone RMP relies heavily on the draft OxyContin (oxycodone extended release tablets) RMP submitted by Purdue Pharmaceuticals to the FDA in May 2002.

All of the mu-opioids are controlled under Schedule II (CII) of the Controlled Substances Act (CSA). Although this schedule is the most restrictive available under the CSA the controls imposed by the CSA apply only to the regulated parties involved in the manufacturing, distribution and prescribing of the product. The patient, household and family members, and in-house healthcare providers are outside the regulatory loop imposed by the CSA. As discussed in our September 2001 consultation, the Sponsor's RMP should not rely upon the controlled status of hydromorphone as a cornerstone.

Our comments and recommendations fall into two categories: A) Prevention, and B) Surveillance and Interventions.

A) PREVENTION

The RMP proposed by the Sponsor focuses on education of the sales force and health care providers including pharmacists and physicians. We recommend that the educational program be expanded.

1. Educational Programs directed to all audiences should include these key messages:

- *Definition of the appropriate treatment population and proper patient selection* Palladone is not for intermittent use; Palladone should only be used by opioid tolerant patients with persistent pain requiring around the clock opioid therapy (Refer to label and PPI.). Pediatric Use: The Label and the RMP are not consistent in describing the target pediatric population.
- *Risks and Safety messages*. Physicians and patients must understand and accept responsibility for appropriate use of Palladone. The risks of overdose-- unintentional or otherwise--should be properly addressed and explained.
- *Risks of abuse, diversion, and theft.* Physicians and patients need to know that the high concentration of hydromorphone in Palladone makes this product a target for theft and diversion.

2. **The completion of the sponsor's physician education program or equivalent training should be considered a requirement for the use of potent opiates including Palladone for persistent, severe, pain and should be made readily available to all potential prescribers.**
   This could be accomplished through an Internet computer-based program. A self-administered examination should assess and provide feedback to the clinician regarding his/her comprehension of the education program. The educational program should include WHO and FSMB Pain treatment guidelines and sample physician patient contracts. Only physicians who have received training in the use of potent opiate analgesic medications should prescribe Palladone.

3. **Physician-patient contract for pain management and treatment with Palladone**
   A contract will help ensure that physicians educate the patient about appropriate use of and the risks associated with the use of Palladone. A mechanism for verifying patient and/or family comprehension should be incorporated at the time of the initial prescription or immediately following the initial prescription. The contract should emphasize the patient's responsibility for safe use of the product including the importance of securing the medicine out of the reach of children and adolescents and others for whom the product has not been prescribed.

4. **Medication Guide**
   If a Medication Guide cannot be required, the sponsor should commit to distribution of the PPI with every prescription.

5. **Lock box or safe provided to patients for the secure storage of Palladone**
   Palladone should be kept away from children, adolescents, and others who might experiment with this potent medication.

6. **Child safe container**
   Ensure that every prescription will be dispensed in a child-safe bottle

7. **Inform patients about the Sponsor's central toll-free number which will provide educational information and receive reports of adverse events and product complaints**

8. **All current and future educational materials, including PI and PPI/Medication Guide changes, should be submitted to the Agency for review before they are distributed to the public.**

B) SURVEILLANCE, MONITORING AND INTERVENTIONS

The purpose of surveillance and monitoring is to assess the effectiveness of the Prevention Part of the Risk management program in curtailing abuse and diversion and to trigger intervention when problems are discovered.

The following is recommended:

1. **All reports of abuse, misuse, overdose and diversion should be reported to FDA on quarterly basis.**

2. **The Sponsor should describe how it will monitor for adolescent abuse of Palladone.**

3. **The Sponsor should describe how the RADARS system will capture and determine the prevalence of iatrogenic addiction.**

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/s/

Silvia Calderon
9/17/02 12:07:05 PM
CHEMIST
Review was signed and hand-delivered to HFD-170 on September 12, 2002.

Deborah Leiderman
9/17/02 12:42:54 PM
MEDICAL OFFICER

PURDUE

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431
(203) 588 8000
Fax (203) 588 8850
www.purduepharma.com

September 11, 2002

REVISED PACKAGE LABELING

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care and
Addiction Drug Products
Office of Drug Evaluation 2
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-170, Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

Re: Palladone™ (hydromorphone hydrochloride extended-release) Capsules
NDA #21-044

Dear Dr. McCormick:

Reference is made to the Purdue Pharma L.P. ("PPLP") New Drug Application #21-044 for Palladone™ (hydromorphone hydrochloride extended-release) Capsules submitted to the Agency on December 29, 1998 and to the amendments to this NDA dated March 30, 2001 and March 12, 2002. Also reference is made to your correspondence dated September 10, 2002 containing CMC comments on the cartons and containers.

Enclosed please find representative labeling for Palladone™ (hydromorphone hydrochloride extended-release) Capsules. We have included for your review a copy of the 12 mg container label (L00103 Pallad 12 mg 100s.pdf), the 32 mg blister-card carton (CT00111 Palad 32 mg hud.pdf), and individual blister foil labeling for each of the four strengths (blister layout.pdf). It is our intent to update all the labeling components for all strengths in identical manner as represented. A complete package of the labeling components will be forwarded under separate cover, as required, on or before Friday, September 13, 2002.

If you have any questions, please do not hesitate to contact me by telephone at (203) 588-8365, by fax at (203) 588-6229, or by electronic mail at richard.fanelli@pharma.com.

Sincerely,

Richard J. Fanelli, Ph.D.
Director, U.S. Regulatory Affairs

Enclosure

32 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 11, 2002

TO: Cynthia McCormick, M.D., Director
Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170

THROUGH: Julie Beitz, M.D., Director
Division of Drug Risk Evaluation, HFD-430

FROM: Carolyn A. McCloskey, M.D., M.P.H., Epidemiologist
Division of Drug Risk Evaluation, HFD-430

SUBJECT: Consult: Review of Palladone™/Extended-Release Hydromorphone Revised Risk Management Plan
PID#: D020403

I. EXECUTIVE SUMMARY

This memorandum is in response to a request from the Division of Anesthetic, Critical Care, and Addiction Drug Produces, to review and comment on the revised risk management plan (RMP) for Palladone™, an extended-release hydromorphone capsule, from Purdue Pharma L.P., indicated for [redacted]

The revised RMP includes educational materials and programs for patients, pharmacists and prescribing healthcare professionals in addition to surveillance and intervention plans. This consult will focus on the surveillance and intervention plans.

Most of the surveillance plans rely on existing treatment or law enforcement programs to recruit subjects which may miss those drug abusers or diverters who do not seek or are not required to attend those programs. Most of the surveillance programs do not recruit adolescents and children or these younger subjects are not recruited very well, thus missing those cases at a critical age for changing their behavior. In summary, these surveillance programs are not representative of 1) all types of abusers and diverters, 2) are not representative of all types of abuse or diversion activities and 3) are not representative of all US geographic regions. Much of the surveillance data is obtained from questionnaires which may be difficult to verify. Lastly, none of the advisory boards for these programs include an FDA representative.

The intervention plans are sketchy and only list education followed by audits of promotional activities and "efforts to determine the nature of the outbreaks" including, for illegal activities, providing placebo Palladone™ and working with law enforcement personnel on interventions. More information is needed in terms of identifying various problems of abuse and diversion and describing specific responses to each of those problems. At the very least, the surveillance programs should be used to assess the effect of the educational programs promised at launch of the drug.

II. BACKGROUND

The Palladone surveillance programs are very similar to the Oxycontin surveillance programs proposed by the same sponsor, Purdue Pharma L.P. Please refer to the July 16, 2002 memorandum by Mary Willy, PhD, MPH on the OxyContin RMP for her comments on the surveillance systems.

This memorandum addresses the revised RMP dated July 2, 2002.

III. SUMMARY of REVISED RISK MANAGEMENT PLAN

6 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling/ PROPOSED

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/s/

Sandra Birdsong
9/13/02 02:14:44 PM
CSO
Signed by Carolyn Mc Closkey, Epidemiologist, on 09-12-02. Signed and Entered into DFS for Carolyn Mc Closkey.

Julie Beitz
9/13/02 02:19:37 PM
DIRECTOR

33 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857
Tel:(301) 827-7410

Division Director's Review and Basis for Action

Drug:	Palladone™ Capsules, 12 mg, 16 mg, 24 mg, and 32 mg
NDA:	#21-044
Sponsor:	Purdue Pharma
Subject:	Response to NA letter, 3rd Cycle
Submission Date:	March 3, 2002
Review Date:	September 10, 2002

This memorandum explicates for the file the basis for the Approvable Action to be taken on the NDA 21-044 for Palladone (hydromorphone HCl) for the treatment of moderate to severe pain in patients who are opioid tolerant. The demonstration of safety and efficacy in the population of intended use and the resolution of chemistry deficiencies have been accomplished in this response to the previous NonApprovable letter. The outstanding issues that must be resolved before approval include (1) agreement on the package insert, (2) qualification of the genotoxic potential of the drug substance impurity morphinone, and (3) satisfactory correction of the deficiencies identified during a recent inspection of the manufacturing facility. The division will ultimately work towards voluntary agreement by Purdue Pharma on all the elements of the proposed Risk Management Plan by the time of final approval.

Background:

Palladone is an extended-release oral formulation of hydromorphone hydrochloride in strengths of 12, 16, 24 and 32 mg. The marketing application was first submitted for FDA review on December 28, 1998.

The data submitted in the initial and subsequent application were not capable of demonstrating the effectiveness of hyromorphone hydrochloride in this formulation. Study HD96-0505, using both an active and placebo control, was the only adequate and well-controlled study submitted

during the first cycle in support of efficacy in this application. The two active-control studies using immediate release hydromorphone did not demonstrate a statistically significant difference between the Palladone and the immediate release hydromorphone formulation on the primary outcome measures. The design in a third study was a randomized, double-blind, parallel group, double-dummy, single center study which compared HHER (hydromorphone HCl extended release) to HHIR (hydromorphone HCl immediate release) and placebo for pain in the immediate postoperative period following orthopedic surgery. Patients were initially titrated to acceptable pain control with PCA fentanyl and were then randomized when pain was moderate to severe to HHER (24 mg as 2x12 mg), Dilaudid 6 mg (3 x 2-mg tablets) or placebo. The primary efficacy variable was the amount of rescue medication (given as PCA fentanyl) for each of four time intervals: 0 - 3, 3 - 6, 6 - 12, and 12 - 24 hours. It is significant that only an initial dose of each treatment was given, yet the measurements were taken after the effect of HHIR, based on its pharmacokinetic profile, would not be contributing much, or anything to the effect. Nevertheless at the later time points, 12-24 hours, when there was no expected contribution of placebo and HHIR to analgesia, the differences between the treatments was not clinically or statistically significant. This may have been a function of decreasing need for medication with time—perhaps reflecting the natural history of postoperative pain as seen in this study. An approvable letter was sent to the sponsor stipulating the need for an adequately controlled multiple dose study in the setting of chronic pain.

In response, the sponsor submitted additional data from a multiple dose efficacy study in patients with chronic pain due to osteoarthritis in patients requiring between 8-14 mg hydromorphone equivalent opioids. Again, the results from this study were not definitive, the effect size was small and the protocol was not adhered to in the analysis of efficacy. There was additionally the observation that patients in both treatment groups, both placebo and treatment, demonstrated worsening of their pain. There were methodological and data integrity problems with this study. Therefore the sponsor was issued a NonApprovable letter, again stipulating the need for an adequately controlled multiple dose study in the setting of chronic pain.

Efficacy

The sponsor has responded to this letter by submitting a third placebo controlled study in patients with chronic pain in patients who have been maintained on opioid medication equivalent to up to 60 mg of morphine, for up to one month, that is, a largely opioid tolerant population. A novel design was employed for this study, randomizing patients to placebo or hyromorphone following a stabilization period on hydromorphone IR. Time to emergence of inadequate analgesia (taking into adequate account the discontinuations due to opioid withdrawal AEs), was the primary analysis. The multiple dose study provided an adequate demonstration of efficacy in this chronic pain population.

Safety—nonclinical

There were no unresolved issues from the previous two review cycles. The sponsor has submitted a timeline for initiation of carcinogenicity studies in rats and mice as a Phase 4 Commitment.

An additional problem arose during the current review cycle. An impurity was identified in the drug substance that is considered a structural alert for mutagenicity. Appropriate mutagenicity testing should be performed, and if positive, this impurity should be reduced to a very low level, such as —PPM. The sponsor was made aware of this problem during the review cycle and has agreed to perform the requisite studies.

Safety—clinical

Clinical evaluation of safety was demonstrated in single and multiple dose studies in healthy volunteers in Phase 1, patients in phase 2, and in multiple dose studies involving 568 patients in Phase 3 studies with chronic pain. The nature and intensity of adverse events were typical of the opioid class of drugs. Deaths were reported in the cancer pain population. No unexpected deaths were reported. The safety update and reanalysis of Phase 3 studies did not raise any new safety concerns about this product. The data provided provide evidence for the safety of Palladone in patients with chronic pain who have been maintained on opioid drugs.

Chemistry Manufacturing and Controls

All deficiencies raised in previous submissions have been addressed. The product will be approved with an expiry date of 2.5 years.

EER

An inspection was conducted of the manufacturing site of the drug substance and finished dosage form in August 2002. The former was found to be acceptable. The manufacturing site of the finished dosage form had significant new GMP deficiencies in addition to unresolved deficiencies from inspections in July and April of this year. The Office of Compliance has concurred with the district office to Withhold Approval based on these deficiencies. The Division concurs.

Abuse Liability

The abuse liability of hydromorphone is well known. It is a Schedule II narcotic and carries the highest penalties for diversion.

The extraction of hydromorphone from this formulation has been evaluated and it is clear that with modest chemical support, the pure form of hydromorphone can be obtained from this formulation by IV abusers.

The sponsor was urged to develop a comprehensive risk management program in an effort to minimize the risks of abuse, diversion, and addiction often associated with products such as this.

Risk Management Program (RMP)

The sponsor has been asked to develop a risk management program in an effort to minimize the risk of abuse and diversion that may result from such a product by virtue of its formulation and potency, and hyrdromorphone's track record for abuse in the past. The matter of RMPs for opioid drug products was raised at an open meeting of the Anesthetic and Life Support Advisory

Committee, with ad hoc representation from the Pain Management community as well as former members of the Drug Abuse Advisory Committee. The meeting was held on January 30-1, 2002. There were presentations from DEA and SAHMSA and the Controlled Substances Staff. At this meeting, the prevailing sentiment was to avoid programs that would result in diminished access to opioids by patients suffering from chronic pain. The Division has made every effort to strike a balance between patient access and the public harm that could occur as the result of diversion and abuse of this product. The DEA has been notified that this product is in development of this product and is working with Purdue Pharma to understand the steps that are currently being undertaken to protect the public.

The sponsor has proposed a RMP :

( )

The program was reviewed by the division staff in consultation with the Controlled Substances Staff and the Office of Drug Safety. Recommendation from the Controlled Substances Staff for approval with restricted distribution was not upheld by CDER's upper management and therefore plans to work rather toward an approval with voluntary measures, stressing elements of education, surveillance and effective labeling were undertaken.

The sponsor has accepted the following elements further recommended for the RMP:

- to voluntarily provide all promotional materials to FDA one month prior to implementation, seeking FDA concurrence with these advertisements.

- a Patient Package Insert has been developed in the format of a Medication Guide. The Medication Guide Subcommittee will be consulted regarding the appropriateness of this product for a medication guide, based on the strong recommendation from the Controlled Substances Staff. A means to make this material available to all patients will be further explored with the sponsor.

- Strong labeling which starts with a BOX WARNING, and realistic INDICATIONS, WARNINGS, and description of the potential for abuse and diversion.

- Strengthening of the Child Safety messages, with redundant educational messages aimed at the lay public.

Further suggestions by the Controlled Substances Staff will be conveyed to the sponsor, however many of the suggestions while they may have theoretical benefit, have been untried and therefore have no proven effectiveness as a deterrent to abuse. It is hoped that the sponsor will voluntarily consider some of these suggestions, but they are not a condition of approval.

Additionally the Office of Drug Safety has provided extensive comments on the risk management program, but has not dismissed the efforts of the sponsor, rather raising questions of clarification. These have been conveyed to the sponsor. It is recognized that the surveillance program that has been proposed has limitations, but it is far superior to what has been available to date for any other controlled substance. It will have to be reassessed as information becomes available.

The Risk Management Program is not a condition of approval, however it is expected that the elements that are still under discussion will be resolved before the final approval action is taken.

Action: An APPROVABLE action will be taken based on the Withhold Approval recommendation from the Office of Compliance, due to the extent of the failed inspection. The following elements should be conveyed to the sponsor in the final approvable letter:

1. Provide adequate qualification of the genotoxic potential of the drug substance impurity morphinone (one point mutation assay and one cytogenetic assay with the isolated impurity tested up to the limit doses for each assay). Alternatively, provide a specification (test, test method, and acceptance criteria) and validation for this impurity with a limit of — ppm".
2. Provide satisfactory correction of the deficiencies identified during a recent inspection of the manufacturing facility for this application will be required before this application may be approved.
3. Submit final printed labeling revised that is identical to the enclosed draft labeling and patient package insert.
4. Agreement on all elements of the Risk Management Program should be achieved and the program should be poised for implementation the time of launch.

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/s/

Cynthia McCormick
9/13/02 01:12:30 PM
MEDICAL OFFICER

EMAILED

Food and Drug Administration
Center for Drug Evaluation
and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: September 10, 2002

To: Richard Fanelli	**From:** Sara E. Shepherd
Company: Purdue Pharma	Division of Division of Anesthetic, Critical Care, and Addiction Drug Products
Fax number: 203-588-6229	**Fax number:** 301-443-7068
Phone number: 230-588-8365	**Phone number:** (301) 827-7430

Subject: NDA 21-044

Total no. of pages including cover: 3

Comments: Attached are CMC comments on the cartons and containers. Please revise the labeling and send prior to Sept 13, 2002. Thanks, Sara

Document to be mailed: ☐ YES ☑ NO

NDA 21-044 Palladone™

Blister foil labels:

Increase the prominence and size of the strength and decrease the prominence and size of the blister number. Provide a separation between the strength and the blister #.

Increase the differentiation between different strengths of blister foil labels in the same manner as the carton/bottle labels.

Bottle labels:

Separate Palladone™ and CII and increase the prominence (e.g., bold and black) of CII (21 CFR 1302.04).

Increase the font size for the storage statement, dosage and administration (the patent information can be eliminated).

Insert "Avoid temperatures above 40° C (104° F) [illegible] " after, but separate from the storage statement.

Insert lot no and expiration date.

When the statement is agreed upon with the agency, revise the red triangle statement. Add the revised red triangle on the bottle label for the 12 mg strength.

Carton labels (Blister box 25 capsules):

Separate Palladone™ and CII and increase the prominence (e.g., bold and black) of CII (21 CFR 1302.04).

Insert "Avoid temperatures above 40° C (104° F) [illegible] ." after, but separate from the storage statement.

The patent information can be eliminated.

Insert lot no and expiration date.

When the statement is agreed upon with the agency, revise the red triangle statement. Add the revised red triangle on the bottle label for the 12 mg strength.

Insert label (PPI):--
Note: these will be included in the next version of the label.

Separate CII from the other labeling and increase its prominence (21 CFR 1302.04).

Remove asterisks on 24 mg and 32 mg.

Provide appropriate corrections to replace the symbols — ' and ' —

Description section - Eliminate ' [illegible]

Correct the chemical structure as per USP.

How supplied section – Provide differentiated headings for each strength of the drug product.

Add "capsules" after the 100.

Revise from "capsules per card" to "capsule blisters per card".

Insert "Avoid temperatures above 40° C (104° F) [illegible]" after, but separate from the storage statement.

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/s/

Sara Shepherd
9/10/02 06:00:11 PM
CSO

EMAILED

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: September 10, 2002

To: Richard Fanelli	**From:** Sara E. Shepherd
Company: Purdue Pharma	Division of Division of Anesthetic, Critical Care, and Addiction Drug Products
Fax number: 203-588-6229	**Fax number:** 301-443-7068
Phone number: 230-588-8365	**Phone number:** (301) 827-7430

Subject: NDA 21-044

Total no. of pages including cover: 6

Comments: Attached is the revised PPI. Please comment prior to Sept 13, 2002. Thanks, Sara

Document to be mailed: ☐ YES ☑ NO

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/s/

Sara Shepherd
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CSO

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_____ § 552(b)(5) Draft Labeling

7/11/02

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

DATE RECEIVED: 4/29/02	**DUE DATE:** 7/12/02	**ODS CONSULT:** 02-0105

TO:

Cynthia McCormick, MD
Director, Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

THROUGH:

Sara Shepherd
Project Manager
HFD-170

PRODUCT NAME:	**NDA SPONSOR:**
Palladone (Hydromorphone Hydrochloride Extended-Release Capsules) 12 mg, 16 mg, 24 mg, 32 mg **NDA #:** 21-044	Purdue Pharma L.P.

SAFETY EVALUATOR: Nora Roselle, PharmD

SUMMARY: In response to a consult from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Palladone" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:
DMETS has no objections to the use of the proprietary name, Palladone. In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product. This name, and its associated labels and labeling, must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

/S/

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: 301-827-3242 Fax: 301-443-5161

/S/

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: July 10, 2002

NDA NUMBER: 21-044

NAME OF DRUG: **Palladone** (Hydromorphone Hydrochloride Extended-Release Capsules) 12 mg, 16 mg, 24 mg, 32 mg

NDA HOLDER: Lipha Pharmaceuticals

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170), for assessment of the tradename "Palladone", regarding potential name confusion with other proprietary/established drug names. The sponsor originally submitted the tradename "Palladone —' for review by the Labeling and Nomenclature Committee (LNC) on January 6, 1999. The conclusion of the LNC on August 20, 1999 was as follows:

> "[Regarding Palladone — ', Purdue Pharma brand of hydromorphone ⊏ ⅃ capsules], — ' is a poor suffix choice since it may be confused for the Roman Numeral designation for — and lead to a medication error. — are more conventional choices. Palladone without — was deemed acceptable. [The established name was found to be] unsatisfactory as the USP does not have controlled released capsules as an official dosage form category [and a] recommended established name is hydromorphone HCl extended release capsules."

The Division (HFD-170) issued a letter to the NDA sponsor regarding these recommendations on September 27, 1999. FDA received a response to this letter on October 8, 1999, with objections to these recommendations. A consult for reassessment of this trademark was evaluated by ODS on November 23, 1999. ODS found the proposed proprietary name "Palladone — acceptable. The Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170) responded to the sponsor stating that the suffix — ' may lead to confusion when practitioners attempt to distinguish the products, and therefore should not be registered for use.

PRODUCT INFORMATION

Palladone is the proposed proprietary name for Hydromorphone Hydrochloride Extended-Release Capsules, a Schedule II controlled substance. Palladone is indicated for ⊏ ⅃ Palladone is to be administered once every 24 hours. Palladone will be supplied as 12 mg, 16 mg, 24 mg and 32 mg capsules in bottles of 100 and in unit dose packages of 25 for institutional use. Palladone is contraindicated in situations of significant respiratory depression, especially in unmonitored settings where there is a lack of resuscitative equipment. Patients with severe bronchial asthma, or who have or are suspected of having paralytic ileus should not be treated with Palladone.

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 that sound-alike or look-alike to "Palladone" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. The Saegis[4] Pharma-In-Use database was searched for drug names with potential for confusion. 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 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

An Expert Panel Discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Palladone". 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.

Several product names were identified in the Expert Panel Discussion (EPD) that were thought to have potential for confusion with Palladone. These products are listed in Table 1 (see below), along with the dosage forms available and usual FDA-approved dosage.

DDMAC did not have concerns about the name with regard to promotional claims.

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

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Palladone	Hydromorphone Hydrochloride Extended-Release Capsules, 12 mg, 16 mg, 24 mg, 32 mg	1 capsule once every 24 hours	
Primidone (Brand name is Mysoline)	Primidone Tablet: 50 mg, 250 mg Oral Suspension: 250 mg/5 mL (240 mL)	Initial: 125 mg-250 mg/day at bedtime Usual Dose: 750 mg 1500 mg/day in divided doses 3-4x/day	L/A
Paradione	Paramethadione Capsule: 150 mg, 300 mg	Initial: 900 mg daily Usual Dose: 900 mg – 2400 mg/day in 3-4 divided doses	S/A
Parlodel	Bromocriptine Capsule: 5 mg Tablet: 2.5 mg	Parkinsonism: 30 mg- 90 mg/day in 3 divided doses Hyperprolactinemia: 2.5 mg 2-3x/day Acromegaly: 20 mg-30 mg/day	S/A
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

[1] MICROMEDEX Healthcare Intranet Series, 2002, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed). Martindale: The Complete Drug Reference London Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2002)

[2] Facts and Comparisons, 2002, Facts and Comparisons, St. Louis, MO.

[3] The Division of Medication Errors and Technical Support [DMETS] database of proprietary name consultation requests, New Drug Approvals 98-02, and the electronic online version of the FDA Orange Book.

[4] Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at [illegible]

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Palladone with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 109 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 Palladone (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.

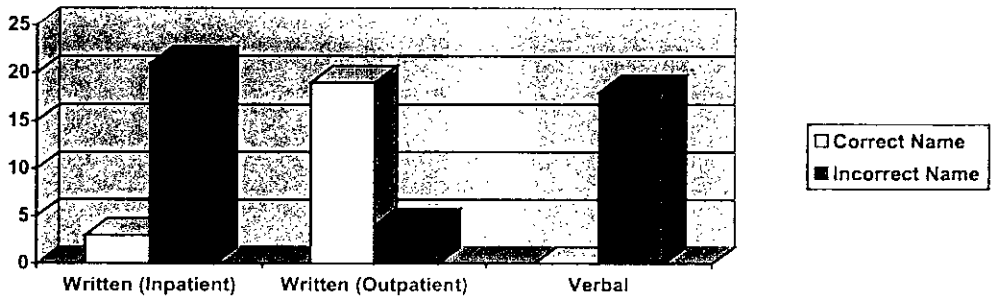
HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient RX: Palladone 24mg Sig 1 po qd #10	Palladone 24 mg Take 1 po qd. Dispense number 10.
Inpatient RX: Palladone 24mg po qd #10	

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted Palladone	Incorrectly Interpreted
Written Inpatient	39	24 (62%)	3 (13%)	21 (87%)
Written Outpatient	39	23 (59%)	19 (83%)	4 (17%)
Verbal Outpatient	31	18 (58%)	0 (0%)	18 (100%)
Total	109	65 (60%)	22 (34%)	43 (66%)



Among the verbal outpatient Palladone prescriptions, none of the respondents interpreted the name incorrectly. Many of the incorrect name interpretations were misspelled variations of "Palladone". Incorrect interpretations included Paladone, Palidone, Pallidone, Palodone, Paladel, Palidin, and Talidone.

When examining the interpretations from the written inpatient prescriptions, 21 of 24 (87%) respondents interpreted the name incorrectly. Incorrect interpretations included Calladone, Callodone, Calladore, Calladene, Salladone, and Lalladone.

In addition, 4 of 23 (17%) respondents from the written outpatient prescriptions interpreted the name incorrectly. Incorrect interpretations included Paladone, Palladine, Pelladene, and Palladon. One respondent from the written outpatient study group commented that the name is "too much like Cordarone".

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Palladone", the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. The products considered having the greatest potential for name confusion with Palladone were Primidone, Paradione, and Parlodel. One respondent from the written outpatient study group commented that the name is "too much like Cordarone".

Primidone is the established name for Mysoline, an anticonvulsant used in the management of grand mal, complex partial, and focal seizures. Primidone is available as 50 mg and 250 mg oral tablets and a 250 mg/5 mL oral suspension. The usual dose of Primidone is 750 mg to 1500 mg daily in divided doses three to four times per day. Primidone can look-alike to Palladone in that each name contains similar letter combinations and three syllables. Both drug names contain the ending "done". However, Primidone and Palladone have completely different strengths and dosing regimens. Primidone is available as 50 mg and 250 mg oral tablets while Palladone will be available in 12 mg, 16 mg, 24 mg, and 32 mg capsules. Primidone is dosed as 750 mg to 1500 mg daily in three to four divided doses while Palladone is dosed as one capsule once daily. In addition, both drugs have completely different indications for use (seizures vs. pain). Thus, due to differences in strength, dosing regimens, and indications for use, the risk of confusion between Primidone and Palladone is minimal.

Paradione (Paramethadione) is an anticonvulsant used only for the treatment of refractory absence seizures. It is not useful for other seizure types and may worsen generalized tonic-clonic seizures. Paradione is a prescription medication available as 150 mg and 300 mg oral capsules. The usual dosage of Paradione is 900 mg to 2400 mg given in three to four divided doses a day. Paradione and Palladone have sound-alike similarities to one another. Paradione and Palladone each have similar sounding prefix letter combinations ("para" vs. "palla"). Likewise, the two name endings also have similar sounds ("dione" vs. "done") which may aid in confusion. However, Paradione and Palladone have different directions for use. Paradione is usually prescribed as several capsules given three to four times a day and Palladone is prescribed as one tablet once a day. In addition, both drugs have different strengths (150 mg and 300 mg vs. 12 mg, 16 mg, 24 mg, 32 mg) and indications for use (seizures vs. pain). Paradione and Palladone have completely different indications for use, dosage strengths, and dosing schedules. The likelihood of confusion between the two drug products is minimal.

Parlodel (Bromocriptine) is a medication used in the treatment of Parkinson's disease, prolactin-secreting pituitary adenomas, and acromegaly. Parlodel is available in a 2.5 mg tablet and a 5 mg capsule. The usual daily dose of Parlodel in the treatment of Parkinsonism is 30 mg to 90 mg per day in three divided doses. Patients being treated for hyperprolactinemia are usually given 2.5 mg two to three times a day. The usual dose of Parlodel in the treatment of acromegaly is 20 mg to 30 mg daily. Parlodel and Palladone have similar sound-alike characteristics. Both drug names contain three syllables and have similar prefix and suffix letter combinations ("par" vs. "pal" and "lodel" vs. "ladone"). Parlodel and Palladone are both oral medications but do not share overlapping dosing schedules or drug strengths. The risk of confusion between Parlodel and Palladone is minimal.

One respondent from the written outpatient study correctly interpreted the name to be "Palladone", but commented that the name is "too much like Cordarone". Cordarone (Amiodarone) is an antiarrhythmic indicated for the treatment of recurrent ventricular fibrillation and recurrent hemodynamically unstable ventricular tachycardia when life-threatening ventricular arrhythmias have not responded to doses of other antiarrhthymics or when other agents could not be tolerated. Both Palladone and Cordarone have three syllables and rhyming endings ("done" vs. "rone"). Cordarone is supplied as 200 mg oral tablets and as 50 mg/mL (3 mL) ampuls for intravenous use. The usual oral daily loading dose for the treatment of ventricular arrhythmias is 800 mg to 1600 mg for one to three weeks, with a usual maintenance dose of 400 mg daily (two tablets daily). Cordarone infusions have a usual loading dose of 150 mg over the first 10 minutes, then 360 mg over the next 6 hours. The usual maintenance infusion dose if 540 mg over a remaining 18 hours. Cordarone is contraindicated in patients with severe sinus-node dysfunction, causing marked sinus bradycardia, second- and third-degree atrioventricular block, and when episodes of bradycardia have caused syncope. Cordarone is associated with toxicity and should only be used in patients with life-threatening arrhythmias. Cordarone use has been associated with pulmonary toxicity, liver injury, worsened arrhythmia, and vision loss. Cordarone and Palladone differ in strength (200 mg tablet and 50 mg/mL injection vs. 12 mg, 16 mg, 24 mg, 32 mg capsules), indication for use (ventricular arrhythmia vs. pain), daily maintenance dosing regimen (two tablets daily for Cordarone vs. one capsule daily for Palladone), and total daily dose which help decrease the risk for confusion between the two drug products.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In review of the blister label, container label, carton and insert labeling and has focused on safety related issues relating to possible medication errors. DMETS has identified several areas of possible improvement which might minimize potential user error.

A. BLISTER LABEL (Blister Foil Label)

1. Revise the established name to read "capsule" rather than "capsules" as there is one capsule contained in each blister.

2. In order to reduce the potential for confusion, remove the [ ] from the blister label as the number would loose its significance if the blisters were separated from one another. In addition, the prominence of the numbers may cause confusion with the strength.

3. When comparing the blister labels side-by-side they appear very similar. We encourage you to differentiate the blister strengths in the same manner as the carton.

B. CONTAINER LABELS (Bottles of 100 Capsules - 12 mg, 16 mg, 24 mg, 32 mg)

1. The font size of the area including the usual dosage and storage requirements is small and difficult to read. Please revise.

2. According to the package insert, the 24 mg and 32 mg capsules are for use in opioid tolerant patients only. The statement enclosed — ' should be removed from the label of the 16 mg strength or the information in the package insert should be corrected.

C. CARTON LABELING (Blister Box – 25 capsules, Institutional Use)

1. See comment B2.

2. The "CII" symbol on the carton may cause confusion as it looks as if it is part of the proprietary name. Please revise according to 21 CFR 1302.04.

D. INSERT LABELING

DMETS recommends not using abbreviations such as — " and — ' in the wording of the package insert. Abbreviations are not readily understandable to all people reading the package insert and may cause confusion. Please revise.

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name, Palladone.

B. DMETS recommends the labeling revisions as 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.

This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

DMETS 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 301-827-3242.

Concur:

Nora Roselle, PharmD
Safety Evaluator
DMETS
Office of Drug Safety

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Nora L. Roselle
7/11/02 08:06:31 AM
CSO

Alina Mahmud
7/12/02 08:15:10 AM
PHARMACIST

Carol Holquist
7/12/02 08:38:48 AM
PHARMACIST

PURDUE

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431
(203) 588 8000
Fax (203) 588 8850
www.purduepharma.com

July 2, 2002

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care and
Addiction Drug Products
Office of Drug Evaluation 2
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-170, Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

GENERAL CORRESPONDENCE:
RISK MANAGEMENT PLAN

Re: Palladone™ (hydromorphone hydrochloride extended-release) Capsules
NDA #21-044

Dear Dr. McCormick:

Reference is made to the Purdue Pharma L.P. ("PPLP") New Drug Application #21-044 for Palladone™ (hydromorphone hydrochloride extended-release) Capsules submitted to the Agency on December 29, 1998 and to the amendments to this NDA dated March 30, 2001 and March 12, 2002.

Reference is also made to our July 17, 2001 submission of a proposed Risk Management Plan for Palladone™. Enclosed is a revised Risk Management Plan, which has been updated based on comments PPLP has received from the Division over the past year, including comments received on the Risk Management Plan for OxyContin® Tablets (NDA #20-553).

As requested by Sara Shepherd, we are enclosing four (4) complete copies of the Risk Management Plan, as well as an additional 4 desk copies without the appendices.

We would like to discuss this plan with you at your earliest convenience. If you have any questions, please do not hesitate to contact me at (203) 588-8365.

Sincerely,

Richard J. Fanelli, Ph.D.
Director
U.S. Regulatory Affairs

Enclosure

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, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Purdue Pharma L.P.	July 2, 2002
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
(203) 588-8000	(203) 588-6229
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
One Stamford Forum Stamford, CT 06901-3431	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(if previously issued)* NDA #21 044

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
hydromorphone hydrochloride	Palladone™ Capsules

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
4,5a-epoxy-3-hydroxyl-17-methylmorphinan-6-one-hydrochloride	HHER

DOSAGE FORM	STRENGTHS	ROUTE OF ADMINISTRATION
capsules (extended release)	12, 16, 24 and 32 mg	oral

(PROPOSED) INDICATION(S) FOR USE

[ ]

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (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 A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OR 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 General Correspondence: Risk Management Plan

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

NUMBER OF VOLUMES SUBMITTED 2	THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

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

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

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(k)(3))
- ☐ 18. User Fee Cover Sheet (Form FDA 3397)
- ☐ 19. Financial Information (21 CFR Part 54)
- ☒ 20. OTHER *(Specify)* General Correspondence: Risk Management Plan

CERTIFICATION

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

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211or 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 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 review 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
Richard J Fanelli	Richard J. Fanelli, Ph.D. Director, U.S.Regulatory Affairs	7/2/02

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
One Stamford Forum, Stamford, CT 06901-3431	(203) 588 8365

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
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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

30 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-044

4/19/02

Purdue Pharma
One Stamford Forum
Stamford, CT 06901-3431

Attention: Beth Connelly
Senior Regulatory Associate

Dear Ms. Connelly:

Please refer to your submission dated July 20, 2001, requesting a waiver for pediatric studies for Palladone (hydromorphone hydrochloride extended-release) Capsules.

We have reviewed the submission and do not agree that a waiver of pediatric studies in all pediatric age groups is justified for Palladone, because terminal or certain chronic conditions in the pediatric population require adequate management of moderate to severe pain. We also acknowledge your intent to submit a request for a Written Request to conduct pediatric studies using the active moiety (hydromorphone) in an age-appropriate formulation as stated in your submission.

Accordingly, a waiver for pediatric studies for this application is denied under 21 CFR 314.55 at this time. We recommend you submit your pediatric plan for this modified formula.

If you have questions, please call Sara Shepherd, Regulatory Project Manager, at 301-827-7430.

Sincerely,

{See appended electronic signature page}

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Cynthia McCormick
4/19/02 06:45:29 PM

4/19/02

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
OPDRA, HFD-400, (15B-23) Sammie Beam			HFD-170 (Division of Anesthetic, Critical Care, and Addiction Drug Products), Sara Shepherd	
DATE April 19, 2002	IND NO. -----	NDA NO. 21-044	TYPE OF DOCUMENT Resubmission	DATE OF DOCUMENT March 12, 2002
NAME OF DRUG Palladone (hydromorphine HCL extended release)	PRIORITY CONSIDERATION Low		CLASSIFICATION OF DRUG opioid agonist	DESIRED COMPLETION DATE August 19, 2002

NAME OF FIRM: Purdue.

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	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
- ☐ BIOAVAILABILITY 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 for a name review for Palladone (hydromorphone HCL extended release) Capsules. The PDUFA date for the resubmission is Sept. 13, 2002. If you have any questions or need additional information, please contact Sara Shepherd, Regulatory Project Manager, at 301-827-7430. Thank you for your assistance.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Sara E. Shepherd, Reg Project Manager 4/19/02	☐ MAIL ☐ HAND ■ DFS
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

No attachment needed for this consult 4/19/02

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

/s/

Sara Shepherd
4/19/02 08:40:12 AM

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 26, 2001

To: Cynthia G. McCormick, M.D., Director
Division of Anesthetic, Critical Care
and Addiction Drug Products (HFD-170)

Through: Deborah B. Leiderman, M.D., Director
Controlled Substance Staff (HFD-009)

From: Silvia N. Calderon, Ph.D., Interdisciplinary Scientist
Ann-Kathryn Maust, M.D., Medical Officer
Controlled Substance Staff (HFD-009)

Subject: NDA 21-044, Palladone Extended Release Capsules
Sponsor: Purdue Pharma L.P.
Response to Request for Advice on Proposed Risk Management Program and Patient Package Insert

I. BACKGROUND

This memorandum responds to a request for consultation from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170) sent on August 3, 2001, seeking the CSS advice and perspective on the proposed Risk Management Plan and Package Insert for Palladone.

Purdue Pharma L.P. submitted a proposal for a Risk Management Program (RMP) to FDA on July 17, 2001 as requested by the Agency in a teleconference on May 30, 2001. The Agency requested development of a Patient Package Insert as well.

According to the sponsor, the risk management program has been designed to address three areas of concern: 1) risk posed by abuse or diversion of Palladone capsules, 2) risk posed by improper patient selection and 3) risk posed by accidental pediatric exposure.

The primary goals of the risk management program are to be achieved through appropriate labeling and promotion; professional educational programs; monitoring for misuse, abuse, addiction, diversion, and overdose; and appropriate interventions when abuse or risk of abuse has been identified.

II. CONCLUSIONS AND RECOMMENDATIONS

1. The risk posed by accidental pediatric exposure to Palladone capsules, even at the lowest strength available, should be recognized as one of the most important areas of concern. Palladone is 8-10 times more potent than morphine.

   Palladone (hydromorphone hydrochloride extended release) capsules will be available in 12-, 16-, 24, and 32 –mg strengths for oral administration. The availability of high doses of a very potent oral opioid, such as hydromorphone, poses a great safety concern, as well as concerns about the high potential for abuse. A comparison of opioid analgesics with respect to dosage shows that a 1.3 mg dose of hydromorphone administered intramuscularly or subcutaneously is equipotent to 10 mg of morphine administered by the same route, and as potent as 0.1 mg (100 μg) of intramuscular fentanyl. When taken orally, 7.5 mg of hydromorphone are approximately equivalent to 60 mg of oral morphine (Goodman and Gilman). When non-analgesic endpoints such as subjective effects were measured hydromorphone was ten times more potent than morphine (Jasinski et al., 1977). Based on recent experience with abuse and misuse of another sustained release opiate product, we are concerned that the extended release feature of the product could be altered, thus immediately delivering an extremely high dose of hydromorphone.

2. The Sponsor's proposed RMP addresses appropriate labeling and promotion, professional educational programs, monitoring for misuse, abuse, addiction, diversion and overdose, and appropriate interventions when abuse or risk of abuse has been identified.

3. The proposed Risk Management Program, however, fails to adequately address the recognized risks associated with inappropriate patient selection and accidental pediatric exposure. The Sponsor should put in place procedures to assure that availability of the proposed drug product would be limited to patients for whom Palladone will provide meaningful therapeutic benefit over existing treatments.

4. Appropriate labeling and promotion will require consistency and definition of key messages that the label will convey to healthcare professionals and patients. After reviewing the information provided in the "Key Messages" , section 1.1, page 6, of the proposed risk management program, the following is recommended:

   - In the "Proper patient selection messages" subsection, page 6, the message indicating that Palladone 24 – and 32 mg capsules are for use in opioid tolerant patients only, should also define an opioid tolerant patient.

   - In the [redacted] of diversion and abuse messages" subsection, page 6, CHANGE the sentence that states [redacted]

     ]' TO:

[ ]

] Also ADD the following sentence:

[ ]

]

5. Under the [ ] section 2.3, page 8, the Sponsor should strongly remind patients, caregivers and patient's family members, that Palladone contains a very potent medicine in an amount that can be fatal to a child. Therefore this product should be stored out of the reach of children and unused units disposed of appropriately. Also [ ] caregivers should be instructed to take every step necessary to avoid accidental exposure, or inappropriate use.

6. When referring to "Scheduling" (Section 3.1), page 8, the following concepts should be clarified and conveyed appropriately:

   - Explain that the CII symbol represents the scheduling status of the drug and that Schedule II substances are considered to have the highest potential for abuse of all available medications. The CSA Schedule II penalties that result from transfer abuse or diversion of substances in this schedule should be clearly indicated.

   - Although true that Schedule II (CII) is the most restrictive classification available under the Controlled Substances Act (CSA), and raises the overall level of vigilance and surveillance, the controls imposed by this schedule only apply to the regulated parties involved in the manufacturing, distributing and prescribing of the product. The patient, family members and in-house healthcare providers are outside the regulatory loop imposed by the CSA. Therefore the patient as well as caregivers and family members in contact with the patient should be instructed to provide a safe storage place and take adequate precautions to avoid accidental exposure, misuse and diversion of the Palladone capsules.

   - At the end of Section 3.1, page 8, the statement that "...and (2) CII status is expected to reduce the risk of accidental ingestion and prescribing for patients who are not opioid exposed, or in case of the higher strengths opioid non-tolerant" should be removed. Recent experience with OxyContin has shown that the schedule II status of a potent opiate drug product is not a deterrent to misuse.

7. In several parts of the RMP, the Sponsor states that Palladone is indicated for the management of moderate to severe pain. We recommend that [ ] be specified if it is the approved indication. Consider limiting the indication for this very potent opiate to "severe pain."

8. The RMP and the Black Box warning should always include the word in italics [ ] as this is a means to by-pass the extended release feature of the drug product.

9. On page 19, the Sponsor lists what will be reported to the Agency. The following should also be reported: the different types of physicians and healthcare professionals who are prescribing Palladone; reports of abuse/diversion from state drug control authorities and state boards of pharmacy.

Please note that CSS would be pleased to be included in the final edits of the labelling, patient package insert, RMP, etc.

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

/s/

Corinne Moody
10/2/01 04:25:39 PM
CSO

Deborah Leiderman
10/2/01 04:50:53 PM
MEDICAL OFFICER

Silvia Calderon
10/3/01 09:33:38 AM
CHEMIST

11 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

PURDUE

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431
(203) 588 8000
Fax (203) 588 8850
www.purduepharma.com

July 17, 2001

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation 2
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-170, Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

Via Federal Express

SUBMITTED IN DUPLICATE

GENERAL CORRESPONDENCE: RISK MANAGEMENT PROGRAM

Full Desk Copy to Judit Milstein, Project Manager

Re: Palladone™ (hydromorphone hydrochloride extended-release) Capsules
NDA #21-044

DUPLICATE

ORIG AMENDMENT

Dear Dr. McCormick:

Reference is made to your December 29, 1999 approvable letter for the Palladone™ (hydromorphone hydrochloride extended-release) Capsules NDA #21-044, to our March 30, 2001 complete response, and to the Agency's confirmation that an action letter will be issued by October 2, 2001.

Reference is also made to the May 30, 2001 teleconference in which the Division requested that Purdue Pharma (PPLP) submit a Risk Management Plan for Palladone™. Herein, PPLP provides our proposed Palladone™ Risk Management Plan. Included as part of this plan is a draft Package Insert (Appendix 1), which has been revised according to the agreements between the Division and PPLP for alterations to the Package Insert for OxyContin® Tablets (NDA #20-553).

We would be happy to discuss this plan with you at your earliest convenience. If you have any questions, please do not hesitate to contact me at (203) 588-8365.

Sincerely,

Richard J. Fanelli, Ph.D.
Director
U.S. Regulatory Affairs

Enclosure

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, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Purdue Pharma L.P.	July 17, 2001
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
(203) 588-8365	(203) 588-6229
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
One Stamford Forum Stamford, CT 06901-3431	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA #21-044

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
hydromorphone hydrochloride	Hydromorphone Hydrochloride Extended Release Capsules

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
4,5a - epoxy-3-hydroxyl-17-methylmorphinan-6-one-hydrochloride	HHER

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
capsules (extended release)	12, 16, 24 and 32 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
management of moderate to severe pain

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314 94)
☐ BIOLOGICS LICENSE APPLICATION (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 N/A Holder of Approved Application

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

IF A SUBMISSION OR 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 General Correspondence: Risk Management Plan and Revised Package Insert

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

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

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

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

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(k)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* General Correspondence: Risk Management Plan and Revised Package Insert

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, 211or 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 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 review 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]	Richard Fanelli Director, U. S. Regulatory Affairs	7/16/01

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
One Stamford Forum Stamford, CT 06901-3431	(203) 588-8365

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
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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

20 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Electronic Mail Message

Date: 6/13/01 4:16:15 PM
From: Bob Rappaport (RAPPAPORTB)
To: Judit Milstein (MILSTEINJ)
Subject: Re: N21-044 Palladone and indicia

Judit-

I am completely unopposed to their use of the — as part of the indicia, unless there is some way it could work it's way into advertising, which I doubt.

Bob

>NDA 21-044
>Palladone extended-release capsules
>Purdue Pharma
>
>6 month PDUFA date: October 1, 2001
>
>Background:
>On April 6, 2001, correspondence was received from Purdue Pharma with a request for the Agency's
agreement to allow to use the — ' indicia in the Palladone capsules.
he same submission, Purdue
dicates that they agreed to change the established name from Palladone — to Palladone
>extended-release, as requested by the Agency.
>Purdue also assures that they have no intention of using the — indicia in any promotional capacity, but
>rather as a unique identifier for the Palladone extended-release Capsules.
>
>21CFR206 -IMPRINTING OF SOLID ORAL DOSAGE FROM DRUG PRODUCT FOR HUMAN USE-
>indicates that the so called indicia by the applicant is an imprinted form of the dosage form.
>
>21CFR206.10 (a) indicates that " a code imprint is required that, in conjunction with the product size,
>shape, and color permits the unique identification of the drug product"
>
>21CFR206.10 (d) indicates that "a code imprint means any single letter or number or any combination of
>letters and words...assigned by a drug firm to a specific drug product"
>
>Based on the CFR definitions, Purdue can legally use — ' for their indicia. However, based on the history
>of the name "Palladone extended-release" product, some reviewers feel that the ' — ' imprint in the
>dosage form is misleading.

estion:
he imprint (indicia) that reads — " acceptable?
>
>Please, justify if you consider that it is not acceptable.

lladone extended-release capsules
rdue Pharma

nonth PDUFA date: October 1, 2001

ckground:
April 6, 2001, correspondence was received from Purdue Pharma with a request for the Agency's reement to allow to use the — ' indicia in the Palladone capsules. In the same submission, Purdue licates that they agreed to change the established name from Palladone —to Palladone extended-ease, as requested by the Agency.
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CFR206 -IMPRINTING OF SOLID ORAL DOSAGE FROM DRUG PRODUCT FOR HUMAN USE- licates that the so called indicia by the applicant is an imprinted form of the dosage form.

CFR206.10 (a) indicates that " a code imprint is required that, in conjunction with the product size, ape, and color permits the unique identification of the drug product"

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estion:
the imprint (indicia) that reads ' — acceptable?

ease, justify if you consider that it is not acceptable.

anks
dit
7440

Extie -

Electronic Mail Message

Date: 6/13/01 12:12:13 PM
From: John Jenkins (JENKINSJ)
To: See Below
Subject: Re: N21-044 Palladone and indicia

Judit

I am not thrilled by the idea of them using — for the indicia for this product. However, I think our regulatory basis for objecting is weak (if there is a basis at all). I personally have never paid much attention to the indicia on tablets/capsules for products that we are reviewing and I suspect that there are other approved products with indicia that we might prefer not be used but to which we have not objected. We must recall that our basis for objecting to the Palladone — name is also weak. I would prefer that they not use this indicia, I would propose [ ] as an alternate, but I don't think I would refuse to approve the product if they insist on —

I have not seen any other opinions expressed and would like to know what others on the review team think.

John

To: Judit Milstein (MILSTEINJ)
To: Cynthia McCormick (MCCORMICKC)
To: Bob Rappaport (RAPPAPORTB)
To: Michael Sevka (SEVKAM)
To: Pramoda Maturu (MATURU)
To: Dale Koble (KOBLED)
To: Kathy Haberny (HABERNYK)
To: Thomas Papoian (PAPOIANT)
To: Shinja Kim (KIMSH)
To: Suresh Doddapaneni (DODDAPANENIS)
To: Thomas Permutt (PERMUTTT)
To: John Jenkins (JENKINSJ)
To: Cathie Schumaker (SCHUMAKER)
To: Judit Milstein (MILSTEINJ)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857
Tel:(301) 827-7410

Division Director's Review and Basis for Action

Division Director:	Cynthia G. McCormick, MD Director, Division of Anesthetic, Critical Care, and Addiction Drug Products
Date:	October 4, 2000
Drug:	Palladone (hyromorphone hydrochloride extended-release) 12, 16, 24, and 32 mg capsules
NDA:	# 21-044
Sponsor:	Purdue Pharma, L.P.
Subject:	NonApprovable action

This application represents a complete response to an Approvable letter for Palladone (hyromorphone modified release tablets) submitted originally December 29, 1998. Because a finding of efficacy could not be made based on the original application the sponsor was required to conduct an adequate and well controlled trial in the target population. In the response, the applicant provided such a study.

Drs. Sevka (Medical Officer) and Permutt (Mathematical Statistician) reviewed this study and have concluded that the study again does not support an approval action. The trial was a one-month double blind, placebo-controlled add-on trial comparing 12 mg Palladone with Placebo with efficacy measurements obtained during the last two days of week 2 and 4 respectively. Pain was scored on a 0-4 categorical scale, where 0 is "no pain" and 4 is "severe pain". The almost imperceptible difference between the two treatment arms of approximately 0.3 on a 5-point categorical scale was statistically significant at a level of p=0.0259. In this trial there was a large number of dropouts. The prospectively designed analysis to impute scores of dropouts for lack of efficacy carrying forward the worst observation, and for those dropping out for other reasons,

carrying forward the last observation was not performed. Instead a LOCF for all dropouts was used to impute the missing data. The prospective analysis might actually be expected to accentuate the difference between groups since there were more dropouts due to LOE (lack of efficacy) in the placebo group than the treatment group. Nevertheless the analysis was not performed and no justification was provided.

Similarly the prospectively defined treatment by center interaction analysis was not performed, and no explanation was given. As Dr. Permutt points out, the statistical significance of the primary result is sensitive to post-hoc choices of methods. The rationale for deviating from the prospective methods was not addressed.

Overall the effect size was small, the imputed data revealed that of the patients who were treated and did not drop out, did as well on placebo as hyromorphone. For those who dropped out, there was a slightly better pain score in the treatment group as the placebo. The effect size of 0.3 on a categorical scale of 0-4 should be justified as clinically meaningful result.

As one steps back from the statistical methodology, looking at the descriptive data, one can see that the change from baseline to week 2 and then to week 4 demonstrates an overall increase in pain scores across both groups, demonstrating a worsening of pain over the course of the 28 day trial. Patients were very slightly worse in the placebo group than in the treatment group by, again, a factor of 0.3 on a five-point scale. Since patients were withdrawn from IR hyromorphone to treatment with Palladone or Placebo, one could hypothesize that the difference might be due to the fact that the IR formulation was providing better pain relief than the ER formulation.

All in all the results of this study are not definitive and the protocol was not adhered to. . Reanalysis per protocol and justification of an acceptable effect size would be needed before these results could be accepted on face. It is my opinion that these weaknesses will not be resolved by reanalysis, and that an additional study should be performed. It is possible also that the dose tested was not high enough.

However, there were additional issues that render this question a secondary one.

The question of data integrity arose during the review cycle, which ultimately led to a for-cause inspection by DSI and Dr. Sevka of the review team. There was unverifiable primary data, and a failure to adequately maintain an electronic trial of the data elements. On September 21, 2001 the sponsor was presented with a Form FDA 483 describing the deficiencies. The elements that were noted during the inspection included the following:

1. Primary efficacy data (test subject pain evaluations) submitted in support of this study was collected using a computerized "Interactive Voice Response System" (IVR). The IVR software program was not validated at the time of use (7/19 - 11/6/00). The computer system used to store the HMP-3005 study data collected by the IVR software at [redacted] (CRO) failed to provide computer generated, time/date stamped

audit trails of operator actions that created, modified, and/or deleted data to assure their accurate retrieval of study data. This data was stored on the [ ] computer system from 7/19/00 until it was electronically transmitted to Purdue Pharma on 12/22/00 in a SAS file. There was no monitoring by the sponsor of this data while it was collected at [ ] to assure accuracy and completeness.

2. Primary efficacy data collected in study HMP-3005 was transmitted directly to the sponsor (Purdue Pharma) without being retained at the clinical investigator site. The lacked documentation that the clinical investigator and the test subject verified changes made to the study efficacy data.

3. SOP for Verification of Electronic Data Transmissions, CDM-01-03.00 Effective October 27, 1997, Section 2.1, requires that electronic data be re-transmitted to the source in its original format for verification and certification by the source. There is no documentation the electronic data, which were used as the efficacy data (files avepain2.dat and avepain3.dat) in support of Clinical Study HMP-3005 were verified.

4. The — data base which maintains data used in support of Clinical Study HMP-3005 has no electronic audit trail to indicate if the database was changed from "locked" to "unlocked", only the final "lock" date is retained.

5. Changes made to the computerized — ' database software used to maintain electronic data at Purdue Pharma were subject only to "Partial" validation after changes as identified CCR #47 and CCR #15. Change Control documentation lacks sufficient detail to justify the "partial" re-validation in lieu of full system re-validation.

There were sufficient methodological deficiencies and issues of data integrity identified in this study during inspection that the Division judges that these results did not support the use of these data as the sole basis for an approval decision.

The chemistry team has identified stability problems with drug product dissolution. The stability provided did not support the requested shelf life. [

] Reanalysis of some of the batches on stability is also requested. The remaining deficiencies in the AE letter of December 29, 1999 have been addressed.

The product packaging for home use has been certifed by the CPSC to be in compliance with 16 CFR 1700.14(a)(4) for controlled drugs. Additionally the packaging for institutional use has been similarly certified.

The Pharmacology review has recommended carcinogenicity and reproductive toxicology as a Phase 4 commitment. These studies should be underway at this time. There has been ample

time during both review cycles to initiate and even complete some of this work. The sponsor should be advised of this.

The Controlled Substances Staff provided a preliminary evaluation of the proposed Risk Management Program for Palladone, submitted very late in the review cycle. There were a number of points raised, which have the potential to strengthen this program. The comments should be deferred to a future meeting in advance of the next review cycle for full discussion.

In summary, the deficiencies outlined during this review cycle including an unacceptable clinical trial and problems with product stability will require significant attention as in the previous application. Another Approvable action is indicated.

Action: Nonapprovable

The letter should outline the following corrective measures

1. Conduct a new adequate and well-controlled study in the target population for a reasonable duration for a chronic study as noted in the previous AE letter. The protocol should incorporate the measures outlined in the DSI inspection, to allow for confirmation of the electronic data at all stages.
2. Correct the Chemistry deficiencies as detailed in the CMC review relating to product stability
3. Conduct carcinogenicity and reproductive toxicology studies

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

/s/

Cynthia McCormick
10/4/01 02:03:15 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

April 28, 2000

Food and Drug Administration
Rockville MD 20857

Roger W. Croswell, Ph.D.
Vice President Worldwide Regulatory Affairs
Purdue Pharma L.P.
100 Connecticut Avenue
Norwalk, CT 06850-3590

Re: Formal Dispute Resolution Request Regarding Palladone — Capsules (NDA 21-044)

Dear Dr. Croswell:

This is in response to Purdue Pharma's Formal Dispute Resolution Request submitted on March 29, 2000, regarding the Agency's December 29, 1999, approvable letter for NDA 21-044 for Palladone — (hydromorphone hydrochloride extended-release) capsules. In the dispute resolution request, Purdue Pharma asks that two items from the December 29, 1999, approvable letter be reviewed at the Office level as the basis of the appeal:

1. "Whether the studies previously agreed to with the Division and submitted by the applicant in a Section 505(b)(2) application demonstrate the effectiveness of extended release hydromorphone hydrochloride for the same indication already approved for immediate release hydromorphone hydrochloride."

2. "Whether the suffix ' — ' in the name Palladone — is acceptable for this product."

I have carefully reviewed the documents provided by Purdue Pharma in support of the Formal Dispute Resolution Request. I have also consulted with members of the Division of Anesthetic, Critical Care, and Addiction Drug Products (the Division) as well as Agency experts in the issues that were raised in the appeal. The experts I consulted included Dr. Robert Temple, Director, Office of Medical Policy, regarding active-controlled, non-inferiority trials and the draft ICH E-10 guidance document and Dr. Robert O'Neill, Director, Office of Biostatistics, regarding the statistical analysis of Study HD96-0505.

Based on my review of the facts and my consultations with Agency experts, I agree with the Division's position that the data submitted in NDA 21-044 are inadequate to demonstrate the safety and effectiveness of Palladone — The submitted data are, therefore, inadequate to serve as a basis for approval of this extended-release formulation of hydromorphone hydrochloride. I also agree with the Division's position that the proposed tradename "Palladone — is not acceptable. A brief summary of the basis for my conclusions is included below.[1]

[1] For convenience and brevity, I will continue to refer to Purdue Pharma's extended-release formulation of hydromorphone hydrochloride as "Palladone — "in the remainder of this letter.

Demonstration of Safety and Effectiveness

When the Division reviewed the pre-meeting package for the July 28, 1998, pre-NDA meeting for Palladone ™ it was noted that two active-controlled non-inferiority studies had been conducted in support of the application. These two active-controlled, non-inferiority studies were the only phase 3, adequate and well-controlled clinical trials planned in support of the NDA.[2] The Division noted, however, that a single-dose, placebo-controlled study had also been completed and was considered by the Purdue Pharma to be an adequate and well-controlled phase 2 study.[3]

The Division did not consider the studies proposed for the NDA to be an optimal development program to support approval of the extended-release formulation, and such a program would not be considered adequate to support an NDA if it were submitted today. Taking into consideration the advanced stage of the Palladone ™ development program and the fact that the program included at least one placebo-controlled study, however, the Division decided that the studies outlined could support submission of an NDA for Palladone ™ The Division also decided that the application could be approved from a clinical standpoint IF the single-dose, placebo-controlled study convincingly demonstrated a treatment effect, and all other requirements for approval were met. The Division considered the two active-controlled, non-inferiority studies to be supportive of approval as they provided safety data following multiple-dose exposure to the new formulation. These studies were not considered adequate for demonstration of effectiveness of the extended-release formulation.

Unfortunately, at the pre-NDA meeting the Division did not clearly communicate the specific rationale and reasoning that supported the conclusion that the proposed program was acceptable for the submission and filing of an NDA for Palladone ™ This miscommunication apparently left Purdue Pharma with the mistaken impression that the Division agreed with Purdue Pharma's interpretation that the two active-controlled, non-inferiority studies were the primary studies supporting submission and approval of the NDA.

In the dispute resolution request, Purdue Pharma argues that the Division's stated agreement to the development plan at the pre-NDA meeting constituted a "written agreement" in the context of Section 505(b)(4)(C) of the Federal Food, Drug, and Cosmetic Act. While I disagree with Purdue Pharma's conclusions on this point, I would note that the agreement the Division made with Purdue Pharma at the pre-NDA meeting was that the proposed development program would be acceptable for submission and filing of an NDA; i.e., the primary goal of a pre-NDA meeting.[4] It is illogical for Purdue Pharma to assert that such agreement also binds the FDA to approve the application since approval of an NDA is based on review of the actual data

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[2] According to the table of studies contained under Attachment 18 of the March 29, 2000, Formal Dispute Resolution package, the two active-controlled, non-inferiority studies were completed in October 1996.

[3] According to the table of studies contained under Attachment 18 of the March 29, 2000, Formal Dispute Resolution package, the single-dose, placebo-controlled study was completed in November 1996

[4] *In the Formal Dispute Resolution package Purdue Pharma asks that this legal argument not be reviewed as the basis for a decision on this dispute since Purdue Pharma believes that the studies submitted to the NDA meet the statutory requirements for approval of the NDA.*

contained in the NDA once it is submitted for review by the Agency. The complete data from the clinical trials discussed at the pre-NDA meeting had not been submitted to the Agency for review at the time of the pre-NDA meeting, therefore, the Division could only agree that the proposed contents of the NDA appeared adequate for filing. As I noted above, the Division was willing to file, and subsequently did file, the Palladone ™ NDA based on the development program proposed at the pre-NDA meeting.. Thus, the Division kept its agreement with Purdue Pharma. Also as noted above, the Division had concluded that the NDA could be approved from a clinical standpoint IF the data from the single-dose, placebo-controlled study convincingly demonstrated a treatment effect of Palladone ™ Unfortunately, the statistical analysis of the single-dose study using appropriate statistical methodology did not demonstrate such a difference (see below).

I will now address the three studies submitted as the primary basis to support approval of the Palladone ™ NDA, i.e., the two active-controlled, non-inferiority studies (Studies HD95-0801 and HD95-0802) and the single-dose, placebo-controlled study (HD96-0505).

Active-controlled, non-inferiority studies are not considered adequate by the Division or the Office of Drug Evaluation II to support approval of analgesics. The rationale underlying this decision is clearly articulated in the draft ICH E-10 guidance document and has been confirmed in my discussions with Dr. Temple, a primary author of the ICH E-10 document. I refer you to section 1.5 of the draft ICH E-10 guidance document for a complete description of the challenges and pitfalls associated with the use of active-control trails to demonstrate equivalence/non-inferiority of a new drug to an established effective treatment.[5]

A critical requirement for interpretation of an active-control trial in the equivalence/non-inferiority setting is to determine the effect size of the active control relative to placebo in the proposed study population and in studies of similar design. Since the actual effect size of the active control is by design not demonstrated in the trial, it must be determined from historical experience. Once the expected effect size of the active control is determined, a clinically appropriate non-inferiority margin can be determined. The confidence interval of the mean difference between the two active treatments must fall entirely within the limits of the non-inferiority margin in order to support a conclusion that the two active drugs are equivalent/non-inferior. The width of the non-inferiority margin must exclude that the two drugs are actually different from one another by a clinically relevant margin. The width of the non-inferiority margin must be determined in advance based on clinical judgement and the known minimum expected effect size of the active control.

As noted in the draft E-10 guidance document, there are many conditions in which drugs considered effective cannot regularly be shown superior to placebo in well controlled studies, thus the minimum effect size of the active control cannot be determined in the setting of a specific trial. In these cases, it is not possible to adequately interpret an active-controlled non-inferiority study for regulatory approval of a drug.

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[5] Published in the Federal Register on September 24, 1999

The Division has appropriately determined that analgesics are examples of drugs for which the minimum expected effect size versus placebo cannot be adequately and reliably determined. This is based on the fact that there are numerous studies of analgesics that are known to be effective where the analgesic cannot be shown to be superior to placebo. This is thought to be due to the variability of pain over time, inadequate study designs, subjective instruments to measure the level of pain, inadequate power of the study, etc.

Purdue Pharma has not provided data from, or references to, adequate and well-controlled studies comparing immediate-release hydromorphone to placebo that adequately establish the minimum expected effect size of this drug in a comparable patient population to that studied in the two trials. The fact that the active comparator drug is approved for marketing is NOT an adequate substitute for data to establish the minimum expected effect size of the drug versus placebo.

Failure to adequately establish the minimum expected effect size of the active control versus placebo precludes the ability to establish relevant non-inferiority margins to compare the two treatments and renders such active-controlled studies uninterpretable with regard to demonstration of equivalence/non-inferiority. The only way that such studies can be favorably interpreted is if the test drug is demonstrated to be statistically significantly different from the active control in the trial, and such differences were not observed in the two active-controlled, non-inferiority studies included in the Palladone — NDA.[6] Thus the two active-controlled, non-inferiority trials are inadequate as a basis for approval of Palladone — The studies do provide supportive safety information following multiple dosing.

Study HD96-0505 is a single-dose, placebo-controlled trial comparing Palladone — .24 mg to immediate-release hydromorphone 6 mg for pain control over 24 hours following orthopedic surgery. As noted above, the Division was willing to approve Palladone — from a clinical perspective if this study convincingly demonstrated a treatment effect for Palladone — By Purdue Pharma's analysis, both immediate-release hydromorphone and Palladone — were statistically significantly different from placebo for the primary endpoint of rescue fentanyl use in this study. Unfortunately, the FDA statistician determined that the statistical model used by Purdue Pharma was incorrect and underestimated the standard errors of the treatment effects. By the FDA statistician's analysis using a more appropriate statistical model, neither immediate-release hydromorphone nor Palladone — was statistically significantly different from placebo.

In the dispute resolution package, Purdue Pharma provided an expert consultation report from Dr. [redacted] that completely agreed with the FDA statistician's analysis of the data from this study. Quoting from Dr. — report, "The Purdue model incorrectly assumes an AR(1) covariance structure among the repeated measures over time. Conclusions with respect to drug efficacy drawn from the Purdue model may be misleading due to this incorrect assumption." Dr.

[6] It is worth noting that by the FDA's statistician's analysis, immediate-release hydromorphone was not statistically significantly different from placebo in the single-dose, placebo-controlled trial included in the NDA. This observation further supports the Division's conclusion that the minimum expected effect size of the active control, immediate-release hydromorphone has not been adequately determined

— further concluded that an AR(1) + CS covariance structure more accurately represents the data and thus provides a better-fitting model. He states that "analyses based on this model lead to the conclusion that there is an association between each active study drug and fewer rescue pain medication injections. However, the associations are not significant, perhaps due to insufficient power."

To gain a further review of the statistical issues raised by the FDA statistician, I asked Dr. Robert O'Neill, Director of the Office of Biostatistics, to review the Purdue Pharma dispute resolution package and the FDA reviews. I met with Dr. O'Neill on April 27, 2000, to discuss the findings from his review. Dr. O'Neill informed me that he is in complete agreement with the FDA statistician and the sponsor's consultant, [ ], that the statistical model chosen by Purdue Pharma was incorrect because it does not fit the data obtained on subjects in the study. Dr. O'Neill stated that Dr. — ' analysis of the data was very comprehensive and clearly demonstrated that the concerns raised by the FDA statistician were valid.

In the Formal Dispute Resolution package, Purdue Pharma argues that since the statistical model was specified *a priori* it should be accepted without question by the FDA. The statement that Purdue Pharma specified the AR(1) model in advance is not documented in the final statistical analysis plan for Study HD96-0505 as submitted in Attachment 28 of the dispute resolution package. Even if Purdue Pharma did specify the AR(1) model in advance, this is not a valid rationale for FDA to accept the analyses based on this model since the model was in fact incorrect. It would have been more appropriate for Purdue Pharma to pre-specify a STRATEGY for determining a correct model rather than selecting a specific model that turned out to be incorrect. Purdue Pharma's consultant, Dr. — correctly followed such a strategy in his review of the data and his conclusions are in complete agreement with those reached by the FDA statisticians.

For these reasons, I agree with the Division's conclusion that Study HD96-0505 does not support approval of Palladone — [7] Since the active-controlled, non-inferiority studies were uninterpretable due to a failure to adequately establish the minimum expected effect size of the active control, there are no adequate and well-controlled studies to support the approval of Palladone —, and the Division's decision to not grant approval was correct.

As noted in the December 29, 1999, approvable letter, it will be necessary for Purdue Pharma to submit at least one adequate and well-controlled, multiple-dose study that adequately demonstrates superiority of Palladone — versus placebo or another control in order to support approval.

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[7] It is worth noting that in Study HD96-0505, the mean use of fentanyl by patients in the immediate-release and Palladone — treatment groups was very similar throughout the 24-hour observation period. This lack of a difference in rescue fentanyl use is surprising given the expectation that the single dose of immediate-release hydromorphone would not provide significant pain relief over the entire 24 hour period. This observation is puzzling and raises questions about the validity of this model to differentiate the effects of immediate-release versus sustained-release hydromorphone products.

In the Formal Dispute Resolution, Purdue Pharma argued that such studies are not necessary since the NDA was submitted under Section 505(b)2 of the Federal Food, Drug, and Cosmetic Act. Purdue Pharma's statements regarding the data requirements for approval of an extended-release formulation of hydromorphone hydrochloride are incorrect. As correctly noted by the Division and Purdue Pharma, the issue at hand is not the effectiveness of the drug substance hydromorphone hydrochloride as currently marketed in immediate-release formulations. Rather, Purdue Pharma's burden is to demonstrate that the proposed extended-release hydromorphone hydrochloride formulation is safe and effective throughout the proposed 24-hour dosing interval in the intended patient population. In other words, Purdue Pharma must demonstrate that hydromorphone hydrochloride is safe and effective when formulated for extended release over a 24-hour dosing interval, which results in significant alterations to the pharmacokinetic profile of the drug compared to immediate-release formulations. Purdue Pharma has also argued that the safety and effectiveness of Palladone — can be adequately established by showing equivalence/non-inferiority to an approved immediate-release hydromorphone product. As explained above, the FDA considers active-controlled, non-inferiority studies to be uninterpretable for analgesics since the minimum expected effect size of the active control cannot be adequately determined.

Acceptability of Proposed Tradename

In the December 29, 1999, approvable letter, the Division advised Purdue Pharma that the proposed tradename [ ] " was not acceptable. The Division advised that Purdue Pharma consider the tradename "Palladone" as an alternative.[8] I agree with the Division's decisions regarding the proposed tradename.

The primary objection to the proposed tradename "Palladone —" is the — " suffix. The use of a suffix as part of tradename is generally considered acceptable only when the suffix is felt to be necessary to distinguish different formulations of the same drug substance marketed under the same root tradename. When such suffixes are used, they should be informative of the difference between the formulations of the drug substance marketed under the same root tradename. Examples might include the need to indicate that the new formulation is a combination containing a new active ingredient, to highlight an important difference between formulations (e.g., powder versus solution), or to differentiate the dosing interval of an extended-release formulation from the immediate-release formulation. When used, suffixes should be easily interpreted and understood by the health care provider and patient, should not be confusing or misleading, and should not be promotional or fanciful.

With regard to Palladone — there is no other formulation of hydromorphone hydrochloride currently approved and marketed under the tradename Palladone, thus there is no need for a suffix to differentiate the sustained-release product from another product. Should an immediate-release hydromorphone formulation be approved in the future for marketing, and if Purdue

[8] A final review of the acceptability of the tradename "Palladone" will be required immediately prior to approval of NDA 21-044 by FDA. It is possible that approval of other products with sound-alike or look-alike names that may cause medication errors or confusion could result in a final recommendation against the Palladone tradename

Pharma chooses to use the Palladone root tradename for that product, the use of a suffix to differentiate the immediate-release product from the extended-release product may be appropriate.[9]

The " — " suffix is also objectionable since it does not simply differentiate two products (e.g., immediate-release from sustained-release) but also makes an implied promotional claim. The " — " can easily be interpreted to mean [ ]", a claim that has not been substantiated by the adequate and well-controlled trials that are generally required to support such claims.[10] If a suffix were warranted for the extended-release product, and one is not warranted at this time, a more appropriate suffix might be one that clearly describes the extended-release characteristics of the formulation.

I now consider this Formal Dispute Resolution closed. If you would like to discuss any of the issues raised in this letter feel free to contact me directly at 301-827-5920. As outlined in the Dispute Resolution MaPP, if you disagree with the conclusions reached by the Office of Drug Evaluation II you may pursue your appeal to Dr. Murray Lumpkin, Deputy Center Director, Center for Drug Evaluation and Research.

Sincerely,

John K. Jenkins /jma-

John K. Jenkins, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: HFD-170/Division File
NDA 21-044
HFD-170/McCormick
HFD-102/Jenkins
HFD-102/Ripper
HFD-002/Sheehy

[9] This statement assumes that the sustained-release product is approved in advance of the immediate-release product and uses the Palladone tradename.

[10] The market research survey submitted as Attachment 4 to the Formal Dispute Resolution package found that 22% of respondents interpreted — to mean —

DEPARTMENT OF HEAL[illegible] & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-044

FEB 2 3 2000

Purdue Pharma L.P.
100 Connecticut Avenue
Norwalk, Connecticut 06850-3590

Attention: James H. Conover, Ph.D.
Executive Director, U.S. Regulatory Affairs

Dear Dr. Conover:

Please refer to the teleconference between representatives of your firm and FDA on January 24, 2000. The purpose of the teleconference was to address the approvable letter that was issued by the Agency on December 29, 1999 for Palladone (hydromorphone hydrochloride extended-release) capsules.

A copy of our minutes of that teleconference is enclosed. These minutes are the official minutes of the teleconference. You are responsible for notifying us of any significant differences in understanding you have regarding the teleconference outcomes.

If you have any questions, call me at 301-827-7410.

Sincerely,

Debbie Fong, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

CC: NDA 21-044
HFD-170/Division Files
HFD-170/D. Fong/C. Schumaker
HFD-170/C. McCormick
B. Rappaport
M. Scheinbaum
A. D'Sa
P. Maturu
L. Jean
K. Haberny
T. Permutt
M. Klein
HFD-870/R. Uppoor
S. Kim
HFD-700/C. Anello
HFD-715/E. Nevius
T. Permutt
M. Welch

Drafted by: D. Fong 2/22/00
Final: D. Fong DF 2/23/00

FILE NAME: 21-044 (PPLP) TCMM LTR 2-23-00.DOC

GENERAL CORRESPONDENCE (TELECON MINUTES LETTER)

TELECONFERENCE MINUTES

Meeting Date: January 24, 2000 **Time:** 1:30-2:30 p.m.
Location: Parklawn 9B-45 Conference Room
NDA: 21-044
Drug: Palladone (hydromorphone hydrochloride extended-release) capsules, 12, 16, 24, 32 mg
Sponsor: Purdue Pharma L.P.
Indication: [redacted]

Type of Meeting: End-of-Review Teleconference
Meeting Chair: Cynthia G. McCormick, M.D., Division Director
Minutes Recorder: Debbie Fong, Pharm.D., Regulatory Project Manager

FDA Attendees:	Titles:	Offices:
Cynthia G. McCormick, M.D.	Division Director	HFD-170
Ramana Uppoor, Ph.D.	Clinical Pharmacology & Biopharmaceutics Team Leader	HFD-870
Shinja Kim, Ph.D.	Clinical Pharmacology & Biopharmaceutics Reviewer	HFD-870
Albinus D'Sa, Ph.D.	Chemistry Team Leader	HFD-170
Pramoda Maturu, Ph.D., M.B.A.	Chemistry Reviewer	HFD-170
Charles Anello, Sc.D.	Deputy Director, Office of Biostatistics	HFD-700
Edward Nevius, Ph.D.	Director, Division of Biometrics II	HFD-715
Michael Welch, Ph.D.	Acting Deputy Director, Division of Biometrics II	HFD-715
Thomas Permutt, Ph.D.	Biostatistics Team Leader	HFD-715
Debbie Fong, Pharm.D.	Regulatory Project Manager	HFD-170

Purdue Pharma L.P.'s representatives:	Titles:
Beth Connelly	Senior Associate, Regulatory Affairs
Dr. James Conover	Executive Director, Regulatory Affairs
Dr. Roger Croswell	Vice President, International Regulatory Affairs
Dr. Jeff Davidson	Director, Biostatistics
Dr. Stephen Hams	Medical Director
Dr. Lloyd Haskell	Executive Medical Director, Medical Research
Ellen Ingber	Executive Director, Project Management
Dr. Robert Kaiko	Vice President, International Director, Clinical Analgesic Research & Development
Dr. Peter Lacouture	Senior Director Clinical Research, Medical Research
Ben Oshlack	Vice President, Pharmaceutical Development
Dr. Robert Reder	Vice President Medical Director, Medical Research
Dr Jack Schreckengost	Director, Biostatistics
Ruth Swanton	Associate Senior Biostatistician, Biostatistics
Dr Fred Tonelli	Senior Director, Pharmacokinetics and Drug Metabolism

Teleconference Objective:
The primary objective of this teleconference was to address the approvable letter that was issued by the Agency on December 29, 1999. The currently proposed indication is [redacted]

[redacted]

Discussion:
Following introductions, Dr. D'Sa addressed Purdue's questions regarding item 3 of the approvable letter, packaging for bottles of 100s, bottles of [redacted] and blister packages. Dr. D'Sa acknowledged Purdue's intent to provide certification that bottles of 100s comply with the requirements of 16 CFR 1700.14(a)(4) for controlled drugs. He also acknowledged Purdue's intent to not make child-resistant packaging for bottles of [redacted] and blister packages, since they are intended for distribution for institutional use only. Dr. D'Sa informed Purdue that they need to consult the Consumer Product Safety Commission (CPSC) regarding these issues and provide the Agency with the CPSC's requirements for outer packaging and specific labeling for child-resistant packaging.

Dr. Uppoor informed Purdue that we generally support the dissolution specifications proposal they faxed on January 20, 2000, with one minor change to the proposed dissolution specification at t=8 hours, which should be [redacted] However, she noted that we have some concerns regarding stability. Dr. D'Sa made the following points:

1) We are seeing individual failures on stability. Purdue must submit S2 or S3 data to support the failures under [redacted] and under accelerated conditions. If no data exist, then Purdue needs to provide justification why they think they meet the stability requirements.

2) Since there is no [redacted] time point in the stability studies, Purdue must justify and/or collect data to support the specifications at [redacted] The current stability data have [redacted] -hour time points.

3) Purdue must provide individual dissolution data for the clinical lots for the clinical study duration. In all cases, Purdue should clearly state the dissolution media utilized.

Purdue stated that they will get back to us regarding item 1. Dr. D'Sa stated that Palladone should meet specifications throughout the life of the product. Purdue stated that they will submit data related to item 2. Dr. D'Sa clarified that we need individual dissolution data points for item 3

Dr. McCormick stated that the action letter we issued would have been a not approvable letter due to the need for additional trials, however we decided to work with Purdue and issue an approvable letter instead. She noted that trial 99-0201 was mentioned by Purdue and stated that we hope this indicates that a new study is ongoing. She asserted that although the NDA may have been capable of demonstrating efficacy on the surface, the development plan was not ideal. The review of the actual data did not suggest such efficacy. She noted that if Purdue submitted this development plan now, we would have attempted to redirect them. However, at the pre-NDA meeting, Dr McCormick's introduction to the project, it did not seem reasonable to completely rethink their plan. Ultimately, the determination of efficacy rests on the data produced, not just the study designs. She emphasized that no formal written agreement was established regarding the acceptability of the studies.

She stated that we have reexamined the criteria used to approve reformulated opiates and the appropriate regulatory mechanism. This was done as a result of an action that Purdue brought against the FDA regarding the approval of another product with a similar data set and development plan, and active-controlled trials. The Agency has learned a great deal from this experience, and we have taken steps not to repeat the same mistake. To apply a different standard to Purdue's product than we had to, upon Purdue's own action, apply to another company's product, would have been inappropriate.

This was a 505(b)(2) application. Therefore, the mechanism of action or efficacy of hydromorphone IR (or the drug substance) never was in question. The finding of efficacy of hydromorphone was made when the FDA approved Dilaudid in the 1970s. However, this does not mean that hydromorphone is effective in all settings and for all patient populations. Purdue's burden was to demonstrate that the CR formulation is effective, i.e. that changing the pharmacokinetic profile does not affect efficacy. Purdue has not succeeded in proving this is the case. All of these observations have led us to question this Division's prior, albeit brief, practice of accepting active-controlled trials as evidence for efficacy.

We do not simply accept the premises that Purdue proposed, namely that the magnitude of effects of the IR formulation is within the range expected when effective treatments are used. The magnitude of effects described by Purdue is based on a study in which a surrogate endpoint was evaluated in healthy volunteers, and a 1965 study of a small number of patients where the data were never examined by the FDA. Furthermore, the patient populations may not be comparable. The two studies cited do not represent a sufficient sample to allow conclusions to be drawn about effect.

Dr. McCormick stated that patients were converted from a variety of medications There have been innumerable studies in which approved opiates have not demonstrated efficacy, even when compared with placebo. Pain, both chronic and acute, is variable and is measured by gross and subjective tools. Placebo rates are high. In many studies, crossover to half-dose opiates or placebo has resulted in no appreciable difference in visual analog scale scores or requirement for rescue medication This suggests that medications may not be adequately controlling pain, or that chronic pain patients accept a certain level of pain.

Dr. McCormick further stated that both studies had sufficient assay sensitivity to reject Palladone if it were inferior. The criteria Purdue used for non-inferiority were not prospectively established In addition, they were not based on an effect size that came from objective data points in studies which evaluated similar patients in similar settings. Instead, they were arbitrarily selected

Dr. Permutt stated that the model Purdue utilized to analyze the placebo-controlled trial, Study 0805, did not establish differences between treatments. The generalized least-squares method is not robust against mis-specification of the correlation structure; and the correlation structure was in fact mis-specified. The autoregressive structure assumes the correlations of observations decline exponentially to zero as the observations become more separated in time, but the empirical correlations decreased from about — for adjacent observations only to about — or — for widely separated observations, not to zero. As a result, the standard errors of the estimated treatment effects were underestimated, so that the significance of the treatment effects was overstated According to Dr Permutt's calculations, the test drug was not significantly different from placebo in the amount of rescue medication used

Purdue stated that the analysis was performed as specified in the statistical analysis plan. They asserted that the model chosen was based on expectations of correlation for the patient population. They asserted that they were limited to certain types of correlation structures for repeated-measures analyses, namely a first-order correlation structure. They stated that they would be willing to discuss this point further at another appropriate time.

Dr. Permutt noted that he questioned whether or not the model was indeed pre-specified, but this is not of great importance. Pre-specification is a way of handling multiplicity, but multiplicity is not the major issue. It is not like analysis of covariance, when there are equally good methods and the concern is multiplicity and post-hoc choice of methods. The model that Purdue used is not a bad model for estimating treatment effects. However, it is an insufficient model for estimating variance. The model is incorrect, given the actual correlations of the observations. Having pre-specifying the model does not resolve the problem.

Purdue inquired what model of the correlations would be better. Dr. Permutt replied that he was not sure that modeling the correlations within patients was the best approach because the effects of interest were between patients. In his review, however, Dr. Permutt fit a model which is a hybrid of autoregressive and compound-symmetric structures, by adding a random subject effect. It might also be acceptable to use the autoregressive model with a robust estimator of the standard error, such as a sandwich estimator with an unstructured estimate of the covariance matrix in the middle Perhaps the best approach, however, is a t-test, because the estimated treatment means are, in any case, means of independent observations across patients, the observation for each patient being a weighted average of the individual hourly values.

However, Dr. Permutt emphasized that additional calculations or an altered data analysis would not be likely to change his opinion of the significance of the results of this study. He believed that he had already performed the necessary calculation in the course of his review.

Purdue stated that their analysis was established a priori. Dr. Permutt reiterated that pre-specification is not the problem. The data do not substantially support a finding of efficacy. Dr McCormick advised Purdue to state their case in writing, if they believe they have a strong case. However, this would not be resolved in a second teleconference.

Purdue emphasized that the active-controlled studies were sized to establish equivalence. They stated that pain at baseline (5/10) decreased to 2/10 following treatment, which would generally not be observed with placebo in this patient population. Patients were randomized to high-dose, low-dose or same-dose, to look at assay sensitivity. Purdue asserted that the sensitivity of the assay was demonstrated, and adequate active-controlled studies were included in the NDA

Dr. McCormick stated that a small subgroup of patients was not fully analyzed, which Purdue did not acknowledge. Dr. McCormick informed Purdue that a group of seven patients cannot be used to validate a study. Purdue stated that the patients were randomized, but acknowledged that it was a small number of patients

Purdue stated that they had considerable experience in the area of chronic pain, and they thought that active- and placebo-controlled studies were adequate Dr McCormick stated that our experience was quite different from theirs, and we have a larger database established She

reiterated that Purdue submitted results for a small study in patients and a study of healthy volunteers, using a surrogate endpoint.

Dr. McCormick stated that Purdue needs to submit an additional, adequate, well-controlled study. This is their best chance of demonstrating efficacy. They should study the product in a setting of proposed use, preferably in a multiple-dose setting. Since the NDA is a 505(b)(2) application, one such study demonstrating efficacy is acceptable. Dr. McCormick restated that we do not question the efficacy of the IR formulation. However, Purdue needs to establish that the new formulation is effective also. If they prefer, they may appeal the Division's decision.

Dr. McCormick stated that we do not feel that the placebo-controlled study is acceptable. Purdue stated that they did not consider the FDA minutes to be a written agreement of what is acceptable. Although they disagree with our conclusions, their intent is to show equivalence, supported by the placebo-controlled study. Dr. McCormick stated that we view the active-controlled study as safety data, which was not reflected by the previous minutes. Purdue asked if they need to develop a stronger case for the 0505 study. Dr. McCormick informed Purdue that they should instead conduct another study, or appeal the Division's decision. Purdue stated that they will prepare their written response.

Dr. McCormick asked Purdue for the meaning of the — suffix on the proposed name of their product. She informed Purdue that, if they are trying to suggest that their product excels, this would imply a marketing claim and is not appropriate. Purdue stated that the — suffix is intended to indicate the [ ] of the product, i.e. [ ] Dr. McCormick informed Purdue that this is a source of confusion, therefore the — suffix is no longer considered acceptable. Older products using the — suffix may only keep it for a while. Purdue cited recent actions taken on [ ] etc, products that were permitted to retain the suffix [ ] In addition, Purdue stated that confusion of the — suffix with the roman numeral for — is not problematic, since Palladone is not available in a — mg strength. Dr. McCormick stated that we do not consider 1998 actions to be recent. She advised Purdue that fewer such suffices will be permitted in the future.

Purdue inquired if suffices such as [ ] are acceptable, and Dr. McCormick advised them that use of any suffix is problematic. Purdue inquired on the proper mechanism of addressing their concerns, e.g. OPDRA. Dr. McCormick informed them they could submit their proposal for a new name, and the Division would consult OPDRA.

Dr. McCormick informed Purdue that their proposal for a safety update is acceptable as is. Purdue stated that they will include their double-blind study of Palladone versus MS Contin in cancer and non-cancer related pain, in their safety update.

Dr. McCormick adjourned the teleconference at approximately 2:30 p.m.

Action Items:

1. We will provide Purdue Pharma L.P. with a copy of the official teleconference minutes.
2. Purdue Pharma L.P. will submit their written response to the approvable letter.
3. Purdue Pharma L.P. will submit their proposal for a new name, and the Division will consult OPDRA accordingly.
4. Purdue Pharma L.P. will submit their safety update.

Minutes Prepared By: Debbie Fong, Pharm.D. Debbie Fong

Minutes Concurred By Chair: Cynthia G. McCormick, M.D. Cynthia G McCormick MD

CC: NDA 21-044
HFD-170/Division Files
HFD-170/D. Fong/C. Schumaker
HFD-170/C. McCormick
B. Rappaport
M. Scheinbaum
A. D'Sa
P. Maturu
L. Jean
K. Haberny
T. Permutt
M. Klein
HFD-870/R. Uppoor
S. Kim
HFD-700/C. Anello
HFD-715/E. Nevius
T. Permutt
M. Welch

Drafted by: D. Fong 2/16/00
Revised: 2/20/00 per D. Fong; 2/22/00 per C. Schumaker, T. Permutt; 2/23/00 per T. Permutt, R. Uppoor, P. Maturu, A. D'Sa
Initialed by: S. Kim, E. Nevius, C. McCormick 2/23/00
Final: C/M C/ 2/23/00
FILE NAME: 21-044 (PPLP) TCMM 1-24-00.DOC

DFS 4 to DFC 1/4/00

MEMORANDUM OF TELECON

DATE: January 4, 2000

BETWEEN:

Name: James Conover, Ph.D.
Director, Corporate Regulatory Affairs
Phone: 203-854-7280
Representing: Purdue Pharma L.P.

AND

Name: Debbie Fong, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

SUBJECT: **NDA 21-044** (Palladone ~, Telecon request

At 4:30 pm, I left a message for Dr. Conover, in response to his voicemail requesting a teleconference to discuss the approvable letter issued December 29, 1999. I asked him to fax and mail a letter requesting this teleconference, specifying questions and relevant points for discussion for the telecon. I informed him that he may include in his letter, as per his message, that he and his colleagues feel this is an urgent issue. We will process his request as quickly as possible.

Debbie Fong, Pharm.D.
Regulatory Project Manager

cc: Original NDA 21-044
HFD-170/Div. Files
HFD-170/D. Fong

Drafted: D. Fong 1/4/00
Filename: 21-044 (PPLP) TC 1-4-00.doc

TELECON

Df.

DEC 3 0 1999

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care and Addiction Drug Products

MEMORANDUM

to: Division File, NDA # 21-044

from: Cynthia McCormick, MD
Director,
Division of Anesthetics, Critical Care and Addiction Drug Products

subject: Palladone (hyromorphone hydrochloride extended-release) 12, 16, 24, and 32 mg capsules

sponsor: Purdue Frederick Laboratories, Inc. (manufacturer)
Purdue Pharma (distributors)

date: December 29, 1999

This memorandum explicates for the file the basis for the action to be taken on the NDA 21-044 for Pallidone (hyromorphone HCl) for [redacted]

Efficacy

One adequate and well-controlled study using both an active and placebo control (Study HD96-0505) was the only evidence of efficacy submitted in support of this application. As Dr. Rappaport has summarized in his supervisory review of efficacy this trial was unsuccessful in demonstrating the effectiveness of hydromorphone hydrochloride in this modified release formulation for the treatment of moderate to severe pain.

In addition there were two active-controlled trials using an immediate release formulation as the control. As to the active controlled trials, these studies demonstrated no statistically significant difference between the ER and IR formulations on the primary outcome measures of change in VAS for pain from baseline, in use of rescue medication, or on a composite endpoint reflecting both. If there had been some demonstration of superiority of the modified release formulation over this unproven comparator, there would have been a reasonable basis for approval. The difficulty with this application is that the test drug did not demonstrate any difference from the comparator, thus, making any conclusion about its efficacy under these test conditions impossible. The problems commonly cited with this type of study are (1) if both treatments are indistinguishable, there is no test to demonstrate that a statistically significant similarity exists, (2) a poorly conducted trial may inadvertently lead no treatment differences, (3) there is no statistical means of demonstrating that either medication worked if there is no statistically significant difference between them, and (4) an active medication may in a given study and set of circumstances be inactive, and therefore not a valid comparator

An active controlled trial with no demonstrable differences between treatments may have been sufficient in an application submitted under 505(b)(2) in which the reference listed drug was the existing modified release formulation, the efficacy of which would have been demonstrated in adequate and well controlled studies. However, such a product does not currently exist. The referenced drug in this 505b2 application is Dilaudid (hydromorphone immediate release) which may be expected to differ in both its efficacy and safety profile by virtue of its distinctly different pharmacokinetics.

I disagree with the conclusions of the reviewing medical officer and statistician who argue that the efficacy of Palladone can be deduced from the available data. The failure to find a difference between two active treatments in the remaining two studies cannot be accepted as evidence for efficacy as described above.

Study HD96-0505

The only study in this NDA which, by design, was capable of giving evidence of effectiveness of Palladone was the active- and placebo-controlled trial, Study HD96-0505. Here, the treatment in question compared to an active control and a placebo (a lower dose of test drug would have been equally acceptable) should have demonstrated a statistically significant difference between the test drug and either the active control or placebo.

The design here was a randomized, double-blind, parallel group, double-dummy, single center study which compared HHER (hydromorphone HCl extended release) to HHIR (hydromorphone HCl immediate release) and placebo for pain in the immediate postoperative period following orthopedic surgery. Patients were initially titrated to acceptable pain control with PCA fentanyl and were then randomized when pain was moderate to severe to HHER (24 mg as 2x12 mg), Dilaudid 6 mg (3 x 2-mg tablets) or placebo. The primary efficacy variable was the amount of rescue medication (given as PCA fentanyl) for each of four time intervals: 0 - 3, 3 - 6, 6 - 12, and 12 - 24 hours. It is significant that only an initial dose of each treatment was given, yet the measurements were taken after the effect of HHIR, based on its pharmacokinetic profile, would not be contributing much, or anything to the effect. Nevertheless at the later time points, 12-24 hours, when there is no expected contribution of placebo and HHIR to analgesia, the differences between the treatments was not clinically or statistically significant. This may be a function of decreasing need for medication with time-- perhaps reflecting the natural history of postoperative pain as seen in this study.

Dr. Permutt, in his statistical review and analysis, has questioned the methods used by the sponsor to obtain significant results in this study. Even if one were to overlook the fact that there were not likely well-defined, and certainly not well-documented prospective analysis plans for this study and assuming that what was done was prospectively defined, the very analysis method chosen was not appropriate. As discussed by Dr. Permutt in his review and detailed in the appendix to his review, the proposed analysis by the sponsor was incorrect, and when the appropriate statistic is applied such as the two-sample t-test or the mixed effects repeated measures analysis of variance using a more plausible clinical assumption, the results were not

statistically significant. The sponsor performed a generalized least squares test as part of a mixed-effects, repeated measures analysis of variance. Dr. Permutt describes that analysis as, "...not especially advantageous for testing treatment effects in a parallel-group study because the treatment effect is a between subjects factor...It has been incorrectly applied in this case; the standard errors of the estimated treatment effects have been grossly underestimated; and the significance levels have therefore been dramatically overstated." The assumption made by the sponsor in this analysis was that measures in a single patient obtained at proximal points in time are highly correlated, and that this correlation approaches zero rapidly over time. That assumption is shown not to be correct during the study. While postoperative pain attenuates over time, it is quite clear from the use of the fentanyl rescue use and from the pain scores obtained during the study that it is not gone within 24 hours. When another assumption is substituted, in this model, that the effects continue to be correlated, attenuate over time, but do not become rapidly independent of each other with each interval, the statistical significance is lost.

Even if one were to set aside the statistical arguments, intuitively, if one looks at fentanyl use in the latter intervals of the study, there is no difference between the groups when one might expect the difference to be greatest, that is when there is no longer hydromorphone IR on board.

Clearly study HD96-0505 cannot be accepted as a positive study.

Having recently reviewed the standards for approval for modified release opiates, the following possible courses meet the regulatory standards for hydromorphone, the immediate release product which was the subject of a "paper NDA" in the 1970's.

1. Perform two adequate and well-controlled studies, as would be required in an application under 505(b)(1), with assay sensitivity—demonstrating a statistically significant difference from a comparator, such as placebo, an active control, or a different dose of the test product.

2. Using an approved IR formulation of hydromorphone as a reference listed drug, submit an application under 505(b)(2). Unless there is good scientific evidence to rule out the pharmacokinetic profile as being a factor in producing the clinical effect, it can't be ignored. Thus, assuming that the SR formulation (the product to be tested) and the IR formulation (the reference product) are not bioequivalent, clinical efficacy in the form of a single adequate and well-controlled study with assay sensitivity (as in 1) would be required. This approach would probably apply only to the first modified release formulation. Thereafter, a subsequent modified release formulation could serve as the reference listed drug.

Therefore the sponsor will be required to perform one adequate and well-controlled study demonstrating the superiority of Palladone over either placebo or a dose control. In addition, since the sponsor must provided evidence of effectiveness of hydromorphone extended release at all proposed doses, particularly at the lowest dose.

Safety—nonclinical

As a 505(b)(2) application, the existing data accepted by the Agency for the Dilaudid NDA, the referenced-listed drug, may be applied to the finding of safety. In addition, the sponsor has conducted 30-day toxicity studies in dogs, but without histopathology.

However, neither reproductive toxicity nor carcinogenicity are available from the literature. here were no specific data on carcinogenicity, mutagenicity, or reproductive toxicology in the original hydromorphone NDAs. However, this sponsor has undertaken segment II reproductive toxicology studies in two species, rat and rabbit, which are described in Dr.Haberny's review. There was no fetal toxicity, embryotoxicity or teratogenicity in fetal rats exposed to doses of up to 10 mg/kg/day. In rabbits, at 50 mg/kg/day, approximately 10x the initial human dose there were reports of decreased fetal weights, greater frequency of visceral and external variations and skeletal abnormalities.

Mutagenicity studies were also performed. The Ames test and mouse micronucleus assay were negative with and without metabolic activation, but in the presence of metabolic activation, the mouse lymphoma forward mutation assay was positive. This indicates some slight risk of genotoxicity in humans. Further study is needed to clarify the significance of these findings.

No carcinogenicity was performed, but will be required as a phase 4 commitment.

Safety—clinical

The safety database for Palladone consisted of 343 opiate tolerant patients (272 with cancer and 71 with nonmalignant pain), 173 healthy volunteers, and 44 postoperative patients for a total of 560 subjects exposed. Of these, 78 (27%) patients received medication for more than one month and only one patient received medication for more than 3 months. When evaluating the patient by dose data it is clear that more than one third of the population studied required doses in the range of >30 mg/day. There is sufficient safety data to support doses up to 32 mg as proposed, taken in conjunction with the PK data which rules out the possibility of dose dumping.

The assessment of serious adverse events, deaths and withdrawals due to adverse events did not reveal any unexpected findings. Many of the serious adverse events were a reflection of the patients' underlying disease state. All 28 deaths occurred in patients with cancer and were all readily attributable to the disease progression or complications of treatment.

In general, as outlined in Dr. Scheinbaum's review of safety both in the NDA and safety update, the common adverse events noted in the HHER population and HHIR population were qualitatively and quantitatively similar and typical of opioid analgesics. No gender, age or racial effects were noted. There was no pediatric exposure during this NDA. The sponsor will be expected to fully evaluate this product in pediatric patients.

The finding of safety has been made by the agency for numerous other hydromorphone products. This finding may have been in part based upon the many years of use of this product, and literature reports of pharmacological and toxicological studies. The safety data which was generated in this NDA was less than one would expect for a new NDA, new molecular entity, however, as a 505b2 application and taking into consideration the previous finding of safety of the IR formulation, paucity of any new serious reported adverse events, and literature references to support the requirements under 21CFR314.50(d)(2), the additional safety data provided by this application is sufficient to support the additional finding of safety for this new product.

Biopharmaceutics

This application included sufficient pharmacokinetics evaluation to adequately characterize the new dosage form. Purdue has done a relative bioavailability study creating a "bridge" to the approved hydromorphone IR (Dilaudid) tablet in which the determination of safety and efficacy was made. Because this product represents a new formulation, additional safety and efficacy data were needed.

There are no significant outstanding biopharmaceutics issues, with one exception. There have been a number of proposed dissolution specifications and the most recent dated November 11, 1999 were considered too wide. The dissolution specifications need to be tightened or alternatively if they are accepted, adequate justification will be needed based on existing in vivo data or additional bioequivalence testing performed on actual lots with such dissolution data.

Chemistry

There are no issues related to the chemistry, manufacture and controls. All inspections were successful.

Regulatory

This application was initially filed as a 505(b)(1) application, but after a review of the application, and teleconference with the sponsor, it was revised to reflect the reliance on literature, safety and efficacy of Dilaudid to a 505(b)(2) application. The appropriate patent certification is in place and the appropriate relative bioavailability study was already submitted.

Summary

While I disagree with the conclusions of the review team that the sponsor has demonstrated the effectiveness of hydromorphone hydrochloride 12, 16, 24, and 32 mg controlled-release capsules, however, given the long track record of hydromorphone as an analgesic, and its bioavailability in this dosage form over 24 hours, it is expected that with a more effectively designed trial to evaluate at a minimum the lowest dosage form throughout the dosage period and in a multiple dose setting and in the absence such widespread use of rescue medication to mask the analgesic effect, the appropriate findings may be demonstrated. The sponsor must, then, perform an additional adequate and well-controlled study in the setting of chronic pain, preferably with multiple dosing, that demonstrates superiority over placebo or an other control in order to establish the efficacy of its product.

Phase 4 Commitments

Upon resubmission of the NDA, the sponsor will be required to commit to carcinogenicity studies— [redacted], further elaboration of the mutagenicity of the produc, and studies in pediatric population. This latter commitment may be made in the form of a written request for pediatric exclusivity. These will not be necessary at this time.

Action

The sponsor will be issued an approvable letter detailing the deficiencies and corrective actions. These are summarized on the next page.

Deficiencies

1. The data submitted in this application do not demonstrate the effectiveness of hydromorphone hydrochloride 12, 16, 24, and 32 mg extended-release capsules. Study HD96-0505, using both an active and placebo control, was the only adequate and well-controlled study submitted in support of efficacy in this application. While on the surface and by your report, this study appeared to provide the necessary statistical evidence of superiority of hydromorphone over placebo based on the chosen methods, you have not provided adequate rationale for the identity of the final methods and how these methods were chosen and applied to the analysis of the primary endpoint, fentanyl consumption. The generalized least-squares test applied as part of a mixed-effects, repeated-measures analysis of variance has been incorrectly applied; the standard errors of the estimated treatment effects have been underestimated and the significance levels have therefore been overstated. In our analysis we do not concur with you conclusions and do not agree that Study HD96-0505 provides evidence of the effectiveness of this new formulation of hydromorphone.

   The two active-control studies using immediate release hydromorphone did not demonstrate a statistically significant difference between the Palladone and the immediate release hydromorphone formulation on the primary outcome measures. Since the test drug did not demonstrate any difference from the comparator, any conclusions about its efficacy under these test conditions are speculative.

   You must perform at least one adequate and well-controlled study in the setting of chronic pain, with multiple dosing, that demonstrates superiority over placebo or another control in order to establish the efficacy of your product. In addition, evidence must be provided to support the effectiveness of all proposed doses, particularly the lowest dose, 12 mg for the duration of the dosing interval.

2. The dissolution method you proposed is acceptable. However, your proposed dissolution specifications dated November 11, 1999 (Table 1) are considered too wide and are not acceptable. The dissolution specifications need to be tightened.

Table 1: Dissolution Specifications—All four proposed strengths of Palladone — [redacted] Capsules

Time (hours)	Lower limit (%)	Upper limit (%)
2	[redacted]	
8		
[redacted]	[redacted]	

However, if you would like to use the November 11, 1999 proposal as the final dissolution specifications, then you must provide adequate justification for your proposed specifications, based on existing in vivo data or additional bioequivalence testing performed on actual lots with such dissolution data.

3. Provide certification that the packaging used in the stability studies and the to-be-marketed product is in compliance with 16 CFR 1700.14(a)(4) for controlled drugs.

4. The established name, hydromorphone hydrochloride controlled-release capsules, must be revised to hydromorphone hydrochloride extended-release capsules, to comply with the USP/NF compendial standards.

5. The name Palladone ™ is unacceptable. You may wish to retain the name Palladone without the ™ suffix.

Cc:
Original NDA 21-044
HFD-170/Div. Files
HFD-170/C. McCormick
B. Rappaport
D. Fong

MEMORANDUM OF TELECON

date to BFS 12/29/99 BF
+to DC

DATE: December 28, 1999

BETWEEN:

Name: Beth Connolly
Senior Associate, Regulatory Affairs
Phone: 203-854-7289
Representing: Purdue Pharma L.P.

AND

Name: Debbie Fong, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

SUBJECT: **NDA 21-044** (Palladone —) Pending action/AE letter

I called Ms. Connolly at 3:30 pm, to inform her that we were canceling our teleconference to discuss our action on NDA 21-044, originally scheduled for 3:30 pm today. I informed her that we plan to take an approvable (AE) action. We are currently finalizing the letter, and we will fax it to them by tomorrow. Ms. Connolly inquired about the nature of the issues. I advised her that once she and her colleagues have time to review the letter and the issues involved, she can call me next week to set up a teleconference to discuss their questions. We prefer to have everything in writing first, prior to having a detailed discussion.

Debbie Fong, Pharm.D.
Regulatory Project Manager

Fong

MEMORANDUM OF TELECON

DATE: December 21, 1999

BETWEEN:

Name: Jim Conover
Director, Regulatory Affairs
Phone: 203-854-7280
Representing: Purdue Pharma L.P.

AND

Name: Debbie Fong, Pharm.D.
Regulatory Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

SUBJECT: **NDA 21-044** (Palladone –) User fee goal dates – January 11, 1999 letter

In response to a voicemail message left by Mr. Conover, I left a voicemail message for him clarifying that our letter of acknowledgment issued January 11, 1999 erroneously stated a secondary user fee goal date of December 12, 1999. The correct date should be December 29, 1999, and we apologize for the error.

Debbie Fong, Pharm.D.
Regulatory Project Manager

cc: HFD-170/Original NDA 21-044
HFD-170/Div. File
HFD-170/D. Fong

Drafted: D. Fong 12/16/99
Filename: 21-044 (PPLP) TC 122199.doc

TELECON

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

SEP 2 7 1999

NDA 21-044

Purdue Pharma L.P.
100 Connecticut Avenue
Norwalk, Connecticut 06850-3590

Attention: Beth Kennedy, R.N.
Senior Associate, Regulatory Affairs

Dear Ms. Kennedy:

Please refer to your December 28, 1998 new drug application (NDA) for Palladone — (hydromorphone hydrochloride) controlled release capsules.

Your proposed proprietary and established names for this NDA have been reviewed, and we have the following comments and recommendations:

1. The proposed proprietary name, "Palladone — is acceptable without the '—' suffix. — " is not an appropriate suffix choice, since it may be confused with the Roman numeral designation for – and lead to a medication error. Since "Palladone" itself is a unique proprietary name, a suffix is not necessary to distinguish it from other hydromorphone hydrochloride products.

2. The proposed established name, "hydromorphone HCl controlled release capsules", is unsatisfactory, since the USP does not have controlled release capsules as an official dosage form category. We recommend that you use the established name, "hydromorphone HCl extended release capsules".

Please submit your response to this letter as soon as possible. If you have any questions, contact Debbie Fong, Pharm.D., Regulatory Project Manager, at 301-827-7410.

Sincerely,

Cynthia M McCormick MD

Cynthia G. McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and Addiction
Drug Products, HFD-170
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 21-044
HFD-170/Div. Files
HFD-170/D. Fong/C.P. Moody
HFD-170/C. McCormick/B. Rappaport/M. Scheinbaum/L. Jean/K. Haberny/A. D'Sa/P. Maturu/T. Permutt
HFD-870/R. Uppoor/S. Kim

Drafted by: D. Fong 9/23/99
Revised: 9/23/99 per C.P. Moody and B. Rappaport
Initialed by: C.P. Moody 9/23/99
final:
filename: 21-044 (PPLP) LNC rev let 092399.doc

GENERAL CORRESPONDENCE

FDA/Purdue Pharma L.P./Fax Memo

Date: **September 2, 1999**

To: **Beth Kennedy, R.N.**
Senior Associate, Regulatory Affairs

Fax: **203-851-5229**

Phone: 203-854-7289

From: Debbie Fong, Regulatory Project Manager DF/cpm

This transmission includes 3 pages (including this page)

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED BY APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is ***unauthorized and strictly prohibited.*** If you have received this facsimile in error, **please notify Debbie Fong by telephone at 301-827-7410 immediately**, return it to HFD-170, 5600 Fishers Lane, Rockville, MD 20857 by US Mail.

Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care and
Addiction Drug Products, HFD-170
Room 9B-45 Parklawn Building
5600 Fishers Lane
Rockville, MD 20857

301-827-7410, fax 301-443-7068

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-044

SEP - 2 1999

Purdue Pharma L.P.
100 Connecticut Avenue
Norwalk, Connecticut 06850-3590

Attention: Beth Kennedy, R.N.
Senior Associate, Regulatory Affairs

Dear Ms. Kennedy:

Please refer to your pending December 28, 1998 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Palladone — (hydromorphone hydrochloride) controlled-release capsules.

We are reviewing your submission and have the following comments and information requests:

To satisfy regulatory requirements for submissions of New Drug Applications (NDAs), the NDA must comply with 21 CFR 314.50. As discussed during our teleconference on August 18, 1999, this NDA should have been submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, instead of 505(b)(1). This change should not affect any exclusivity period that may be granted if the NDA is approved.

To effect this change, please submit the following documents to your NDA:

1. Revised Form 356h, specifying that the NDA is being submitted under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (check the box marked 505(b)(2) under the section entitled Application Information), in accordance with 21 CFR 314.50(a)(2)
2. Patents on this drug or use of this drug, in accordance with 21 CFR 314.53
3. Patent certification(s) on any listed drug(s), in accordance with 21 CFR 314.50(i)
4. Information regarding the period(s) of marketing exclusivity, if any, on any listed drug(s). Please refer to 21 CFR 314.108 for further information.
5. Duration of marketing exclusivity to which you believe you are entitled, if any, if this NDA is approved. Please refer to 21 CFR 314.50(j) and 21 CFR 314.108 for further information.
6. List of the sections within your NDA on which you expect this Division to rely during our review, to which you do or do not have right of reference, as defined in 21 CFR 314.3(b).

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, contact Debbie Fong, Pharm.D., Regulatory Project Manager, at 301-827-7410.

Sincerely,

Corinne P. Moody

Corinne Moody
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and Addiction
Drug Products, HFD-170
Office of Drug Evaluation II
Center for Drug Evaluation and Research

E L E C T R O N I C M A I L M E S S A G E

ensitivity: COMPANY CONFIDENTIAL

Date: 20-Aug-1999 04:12pm EDT
From: Dan Boring
BORINGD
Dept: HFD-530 CRP2 S447
Tel No: 301-827-2396 FAX 301-827-2510

O: Nancy Chamberlin (CHAMBERLINN)

C: Jerry Phillips (PHILLIPSJ)

ubject: LNC Consults

Appears This Way
On Original

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	HFD#	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
1229	170	Palladone —	hydromorphone controlled release capsules
ATTENTION: Nancy Chamberlin			

A. Look-alike/Sound-alike

Potential for confusion:

___ Low	___ Medium	___ High
___ Low	___ Medium	___ High
___ Low	___ Medium	___ High
___ Low	___ Medium	___ High
___ Low	___ Medium	___ High

B. Misleading Aspects:

C. Other Concerns:

— is a poor suffix choice since it may be confused for the Roman Numeral designation for — and lead to a medication error. [ ] are more conventional choices.

D. Established Name

___ Satisfactory

XXX Unsatisfactory/Reason

The USP does not have controlled released capsules as an official dosage form category

Recommended Established Name

hydromorphone HCl extended release capsules

E. Proprietary Name Recommendations:

XXX ACCEPTABLE [ ] ___ UNACCEPTABLE

F. Signature of Chair/Date D Boring 8/20/99

Telecon Memo:

Phone	203 854 7485
Date	July 2,1999
NDA	21-044
Sponsor	Purdue Fredrick Irina Privin, Assoc. Dir. Reg Affairs.
FDA	Albinus D'Sa, Ph. D. (Chemistry Team Leader) 7/2/99
Issue	Post-approval CMC proposal for qualification of new drug substance supplier.

Ms. Privin called asking for my comments on a proposal for stability matrix (fax dated June 21, 1999) to qualify a new supplier of the drug substance. I confirmed that this proposal was for post-approval changes and not for the current NDA under review. I told Ms. Privin that the proposal for matrixing the data in the stability protocol was acceptable. However, the issue of determining expiration date was best left to be decided at the time of review. I conveyed that as it appeared in the proposal, [ ] epiration date could not be granted with only [ ] stability data.
The conversation was cordial.

CC HFD-170/div file NDA 21-044
Chemist/MaturuP/D'SaA
CSO/FongD/MoodyC
Div Director/McCormickC

FDA Fax Memo

FEB 19 1999

Date: **February 19, 1999**

To: **James H. Conover, Ph.D.**
Executive Director, Drug Regulatory Affairs and Compliance

From: Nancy Chamberlin, Project Manager

This transmission includes 3 pages (including this page)

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Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care and
Addiction Drug Products, HFD-170
Room 9B-45 Parklawn Building
5600 Fishers Lane
Rockville, MD 20857

301-827-7410 , fax 301-443-7068

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-044

FEB 19 1999

Purdue Pharma L.P.
100 Connecticut Avenue
Norwalk, Connecticut 06850-3590

Attention: James H. Conover, Ph.D.
Executive Director, Drug Regulatory Affairs and Compliance

Dear Dr. Conover:

Please refer to your pending December 28, 1998 New Drug Application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Palladone — (hydromorphone hydrochloride) Controlled-Release Capsules.

We are reviewing the Pharmacokinetic section of your submission and have the following comments and information requests:

Pharmacokinetics:

1. Please provide the % dissolved vs time, plasma concentration vs time, PK parameters, and % absorbed vs time (and convolute dissolution data) for each formulation on a diskette in ASCII or EXCEL format.

2. You are requested to provide rationalization for [redacted]

3. Please provide a summary from the literature, of the extent and nature of protein binding, and in vitro metabolism profile (with respect to cytochrome P450) of hydromorphone.

4. Please resubmit the in vitro study that was done to evaluate [redacted] the product's drug release (IND —) to the NDA.

5. Please provide individual study summaries (include Tables and Figures) on a diskette in MICROSOFT WORD format (e.g. Volume 18).

6. Please submit the data files associated with the population PK-PD studies on a diskette in ASCII or EXCEL format (i.e., HD95-0701, HD95-0801, HD95-0802, HD95-0803).

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Nancy Chamberlin, Project Manager, at (301) 827-7410.

Sincerely,

Cynthia G McCormick MD

Cynthia G. McCormick, M.D.
Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 21-044

Food and Drug Administration
Rockville MD 20857

Purdue Pharma L.P.
100 Connecticut Avenue
Norwalk, Connecticut 06850-3590

JAN 11 1999

Attention: James H. Conover, Ph.D.
Executive Director, Drug Regulatory Affairs and Compliance

Dear Dr. Conover:

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: Palladone — (hydromorphone hydrochloride) controlled release capsules

Therapeutic Classification: Standard (S)

Date of Application: December 28,1998

Date of Receipt: December 29,1998

Our Reference Number: 21-044

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 27,1999 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 29,1999 and the secondary user fee goal date will be December 12,1999.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact Nancy Chamberlin, Consumer Safety Officer, at (301) 827-7410.

Sincerely,

Corinne P. Moody
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and Addiction
Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

IND 38,424

DEC 2 1998

Purdue Pharma L.P.
100 Connecticut Avenue
Norwalk, Connecticut 06850-3590

Attention: James Conover, Ph.D.
Executive Director, DRAC

Dear Dr. Conover:

Please refer to your Investigational New Drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Hydromorphone Hydrochloride Controlled-Release Tablets.

We also refer to the face to face meeting held on July 28, 1998, between representatives of your firm and this Agency.

Enclosed is a copy of our minutes of the meeting.

If you have any questions, please contact Tony Chite, P.D.,Consumer Safety Officer, at (301) 827-7410.

Sincerely,

Corinne P. Moody
Chief, Project Management Staff
Consumer Safety Officer
Division of Anesthetic, Critical Care and
Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

Meeting Minutes:

NOV 16 1998

MEMORANDUM OF MEETING MINUTES

Meeting Date: July 28, 1998
Time: 9:30 a.m.
Location: 3rd Floor Parklawn Room B

Application: IND 38,424 Hydromorphone controlled release capsules

Type of Meeting: FDA-Industry (Purdue Pharma) Meeting
pre- NDA

Meeting Chair: Cynthia McCormick, M.D.

Meeting Recorder: Tony Chite

FDA Attendees:	Titles:	Offices:
Cynthia G. McCormick, M.D.	Division Director	HFD-170
Bob Rappaport, M.D.	Deputy Division Director	HFD 170
Charles Cortinovis, M.D.	Medical Reviewer/Anesthetic	HFD-170
Albinus D'Sa, Ph.D.	Team Leader/Chemistry	HFD-170
Pramod Maturu, Ph.D.	Chemistry Reviewer	HFD-170
Dou Huey Jean, Ph.D.	Team Leader/Pharmacology	HFD-170
Kathleen Haberny, Ph.D.	Pharmacology Reviewer	HFD-170
Suresh Doddapaneni, Ph.D.	Pharmacokineticist Reviewer	HFD-870
Tom Permutt, Ph.D.	Team Leader/Biostatistician	HFD-170
Corinne P. Moody	Chief, Project Management Staff	HFD-170
Tony Chite, P.D.	Project Manager	HFD-170

External Attendees:	Titles:
James Conover, Ph.D	Regulatory Affairs
Robert Kaiko, Ph.D.	Clinical
Peter Lacouture, Ph.D.	Clinical
Jeffrey Lazar, M.D., Ph.D.	Human Pharmacology
William Mallin, MBA	Project Leader
Phil Palermo, Ph.D.	CMC
Susan Rosen, M.D.	Clinical
Stan Stadnicki, Ph.D.	Pharm/Tox
Ruth Swanton, MPH	Statistician

MEETING MINUTES:

A brief presentation was provided as requested.
Hydromorphone HCl has been in human use in the USA for over 50 years.
The dosage strengths are 12, 16, 24, and 32 mg. capsules.
The indication is for [ ]

The sponsor estimates an NDA submission for the fourth quarter of 1998.
The following were the main discussion points of this meeting.

Chemistry:

Sponsor is using melt extrusion technology for this product. All USP grade excipients are used.

The video that was submitted by the sponsor does not qualify as validation document. Batch records are needed. Pre NDA package is otherwise in good shape. Sponsor has sufficient chemistry data for filing NDA at any time.

A [ ] is needed of the batches used. Sponsor agreed to provide process validation.

Sponsor stated [ ] on storage.

Pharmacology:

The pharmacology and toxicology section of the NDA can be supported by a review of the available literature, and the proposed studies on comparative impurity profiles and Segment II reproductive toxicology studies. Mutagenicity studies are also requested to update the label. The sponsor is urged to submit the study reports prior to NDA submission if possible. The proposed label will be evaluated after the study reports have been submitted for review.

Pharmacokinetics:

Sponsor was requested to include dose as a covariate in the population pharmacokinetic analysis. Sponsor was requested to provide a description of the modeling building strategy, model validation approach, and final model structure in the population pharmacokinetics report. In addition, datasets used in the population analysis should be submitted electronically in ASCII format. The sponsor was requested to provide data on pH independence and IVIVC to section 6.0 of the NDA. The sponsor was requested to validate the IVIVC model using the 32 mg strength.
When pointed out that the plasma concentration profile of the product appears to be [ ] instead of a once a day product, sponsor attributed this to colonic absorption and will address this in the NDA.

Clinical: The sponsor provided the Agency with the information on a dosing regimen. Sponsor stated that the Drug is intended for once a day dosing in patients with opiate-dependent cancer pain. Pivotal studies are 35 days, using Dilaudid as the active control. Chronic nonmalignant pain patients are questionable in the inclusion criteria. Rescue medication was short acting Dilaudid. End point: pain intensity & use of rescue medication.

A PK study was done [ ], however the sponsor is not seeking a pediatric indication. The sponsor could not recruit adequately for pediatric trials. If this product is intended for pediatric use, propose that PK and open label safety data be generated, and that the extrapolation from adult studies be considered for efficacy. The drug is not intended to be used in children. The sponsor was encouraged to obtain as much pediatric data as soon as possible. The reason for the [ ] dosage form is intended for use in geriatric patients and patients having difficulty swallowing.

There is a safety database of about 500.

Statistics

The Agency's Statistics Team Leader indicated that the proposed submission is adequate.

CSET The proposed submission is adequate. The Controlled Substance Evaluation Team would like a separate section when the sponsor submits the NDA.

Discussion Issues

Page 18 from section 3 in briefing package

1. We would like to confirm that the approaches described for handling each of the previous FDA requests and Purdue Commitments as described in the preceding pages are acceptable to the Division.

They are acceptable.

2. We would like to confirm that the plan for analyzing and presenting efficacy data in the Integrated Summary of Efficacy (see ISE outline in Tab 6d) is acceptable to the Division.

It is acceptable.

3. We would like to confirm that the plan for analyzing and presenting the safety data in the Integrated Summary of Safety (see 155 outline in Tab 6d) is acceptable to the Division.

It is acceptable.

4. We would like to confirm that the basic organization of the NDA as presented in the draft NDA Table of Contents (see Tab 5) is acceptable to the Division.

It is acceptable.

5. We would like to discuss the Division's position on the need or advisability for Purdue to prepare an electronic submission of any or all of the information to be included in the NDA. We are prepared to provide paper copy as well.

The agency would like electronic submission with one complete archival copy. SAS format is fine for data.

The above questions from the sponsor were addressed and there were no further questions.

Minutes Preparer: Tony Chite

Chair Concurrence: Cynthia McCormick MD

7 PAGES REMOVED. SEE THE ADVISORY COMMITTEE MEETING INFORMATION LOCATED ON THE FDA WEBSITE BELOW:

http://www.fda.gov/ohrms/dockets/ac/

Sept. 9-10, 2003

New Drug Application
Hydromorphone Hydrochloride [ ] Capsules 100 Connecticut Avenue, Norwalk, CT

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

Form Approved: OMB No. 0910-0297
Expiration Date: November 30, 1996

USER FEE COVER SHEET

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

Purdue Pharma L.P.
100 Connecticut Avenue
Norwalk, CT 06850-3590

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

The Purdue Frederick Company
100 Connecticut Avenue
Norwalk, CT 06850-3590

Contact: James H. Conover, Ph.D.

3. TELEPHONE NUMBER *(Include Area Code)*
(203) 853-0123

4. PRODUCT NAME
Palladone ~~—~~ (hydromorphone hydrochloride) Controlled-Release Capsules

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA? [X] YES [ ] NO

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

6. USER FEE I.D. NUMBER
3567

7. LICENSE NUMBER/NDA NUMBER
NDA #21-044

8. 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 BEFORE 9/1/92
[ ] THE APPLICATION IS SUBMITTED UNDER 505(b)(2) *(See reverse before checking box.)*
[ ] AN INSULIN PRODUCT SUBMITTED UNDER 506

FOR BIOLOGICAL PRODUCTS ONLY

[ ] WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION
[ ] A CRUDE ALLERGENIC EXTRACT PRODUCT
[ ] BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92
[ ] AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

9 a. HAS THIS APPLICATION QUALIFIED FOR A **SMALL BUSINESS EXCEPTION**? [ ] YES *(See reverse if answered YES)* [X] NO

b. HAS A **WAIVER** OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES *(See reverse if answered YES)* [X] NO

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
James H. Conover Ph.D.	Executive Director, Drug Reg. Affairs & Compliance	12/1/95

FORM FDA 3397 (12/93)