

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201194Orig1s000

CHEMISTRY REVIEW(S)

NDA 201194

VistaPharm, Inc.

Julia C. Pinto, Ph.D.
Office of New Drug Quality Assessment, Division III

Division of Anesthesia, Analgesia and Addiction Products

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Chemistry Review Data Sheet

Chemistry Review Sheet

1. NDA 201194
2. REVIEW #: 2
3. REVIEW DATE: October 6, 2011
4. REVIEWER: Julia C. Pinto, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

N/A

6. SUBMISSIONS BEING REVIEWED:

Submission(s) Reviewed

Amendment
Amendment
Amendment
Amendment
Amendment

Document Date

January 31, 2011
February 7, 2011
June 9, 2011
July 11, 2011
September 3, 2011

7. NAME AND ADDRESS OF APPLICANT:

Name: VistaPharma
Address: 7265 Ulmerton Road
Largo, Florida, 33771

Representative: John G. Lay, Director Regulatory Affairs
Telephone: 727-530-1633 (jlay@vistapharm.com)

8. Product Drug Code and Name:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): Oxycodone Hydrochloride Oral Solution
- c) Code name/#(ONDQA only):
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: Type 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: FD&C ACT 505(b)(2)

10. PHARMACOLOGICAL CATEGORY:

Treatment of moderate to severe pain where the use of an opioid analgesic is appropriate.

Chemistry Review Data Sheet

11. DOSAGE FORM: Oral Solution
12. STRENGTH/POTENCY: 5mg/5ml
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed
 Not a SPOTS product

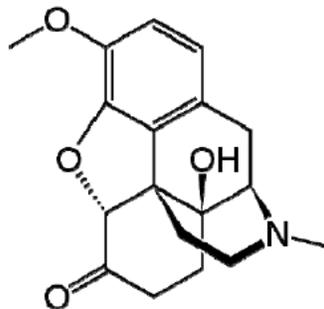
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

- Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-17-methyl-,hydrochloride,(5 α)-.
- 4,5 α -Epxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Molecular Formula: C₁₈H₂₁NO₄.HCl

CAS: 124-90-3

MW: 351.82



17. RELATED/SUPPORTED DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	Code ¹	Status	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	7			Since the manufacturing process is revised and referenced to DMF (b) (4), and the drug substance used in the manufacture of the clinical and marketed batches of drug product is from DMF (b) (4), DMF (b) (4) was not reviewed.
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	Nov 2010	Julia Pinto Rev #1

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	4			
	III		4			
	III		4			
	III		4			
	III		4			
	IV		1	Adequate	12/1/2010	J Pinto, Ph.D. Rev. #1
	III		3,4			

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	105754	Oxycodone HCl Oral Solution 5mg/5ml

18. Status

ONDQA:

CONSULTS/ CMC RELATED	RECOMMENDATION	DATE	REVIEWER
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Chemistry Review Data Sheet

REVIEWS			
Biometrics	NA		
EES	Adequate	June 10, 2010	Office of Compliance
Pharm/Tox	Not Approved pending updated specification for ^{(b)(4)} Impurity	January 14, 2011	Elizabeth Bolan
Biopharm	NA		
LNC	NA		
Methods Validation	NA		
DMET/DDMAC			
EA	Categorical exclusion satisfactory	May 2010	J. Pinto
Microbiology	NA		

Executive Summary Section

The Chemistry Review for NDA 201194**The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

This application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The Office of Compliance has issued an "Acceptable" overall recommendation for all facilities involved in production of the product. The deficiencies noted during the first review have been satisfactorily addressed. The revised specification tables for the drug substance and drug product have been provided and a calibrated dosing cup is added to the 500ml bottle. Labeling has all the required CMC information. However the release testing of the drug product did not include testing for *Burkholderia cepacia*. The Sponsor has committed to testing the commercial scale batches for *Burkholderia cepacia* using their in-house method. Therefore, from a quality perspective, this NDA is recommended for approval with the following Phase 4 commitment.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable-

The Sponsor has committed to the following PMC:

- 1) VistaPharm commits to conducting a microbial challenge test to understand if our preservative matrix would eliminate the *Burkholderia cepacia*.
- 2) If the preservative matrix does not eliminate the *Burkholderia cepacia* VistaPharm commits to adding *Burkholderia cepacia* to our current regulatory and stability specification, this information would be submitted via post approval supplement.
- 3) If the challenge eliminates the *Burkholderia cepacia*, the data will be submitted via post approval supplement with no changes to the current regulatory specification or stability protocol.

II. Summary of Chemistry Assessment**A. Description of Drug Substance and Drug Product:**

The drug substance used in this product is oxycodone hydrochloride and is referenced to DMFs (b) (4) (where it is made). Under DMF (b) (4) the process to produce the drug substance, also produced an (b) (4). The (b) (4) is an (b) (4) that is (b) (4) oxycodone. However, to limit the amount of (b) (4) that forms in the process, (b) (4) modified their process, under DMF (b) (4), to include an additional (b) (4). The new process and improved quality drug substance, having minimal (b) (4) present, is the subject of the second (b) (4) DMF (b) (4). Therefore, the drug substance used in the manufacture of the

Executive Summary Section

clinical and commercial batches of drug product is that obtained under DMF (b) (4). The drug substance specifications provided during the course of the first review, reflected the higher limits of (b) (4), under DMF (b) (4). Further, testing and a specification for heavy metals, had also been requested in the first review cycle, as part of the release testing of the Drug Substance, since (b) (4) during manufacture of the DS. The Sponsor has provided updated limits and justifications for both the drug substance and drug product specifications. The DS is stored in a single (b) (4) bag and placed inside a heat-sealed foil bag. The retest period is (b) (4). The EES of the DS is also acceptable (see review #1 for OC report).

The drug product (DP) is manufactured by Vistapharm in Largo, Fl. The EES is acceptable (see review #1 for OC report). The DP is formulated as a 5mg/5ml oral red solution. The formulation includes sodium benzoate (b) (4), red colorant and raspberry flavoring. It is manufactured on a scale of (b) (4). It will be packaged in two configurations, 5ml unit dose cups and 500ml HDPE bottle. A dosing device was not provided for in the original NDA submission. Upon discussions between the division and the Applicant, it was agreed to provide a calibrated cup to be included with the 500ml bottle. The specifications and calibration of the dosing cup has been provided and is acceptable. Stability studies demonstrated that the product is stable, stored in both configurations at 25°C/60%RH or at 40C/75%RH. An expiry of 24 months for the 500ml bottles and 18 months for the unit dose cups, is granted.

B. Description of How the drug is intended to be used:

The proposed drug product is an immediate release oral solution containing 5mg/5ml of oxycodone HCl. It is intended for use in the treatment of moderate to severe pain where the use of an opioid analgesic is appropriate.

C. Basis for Approvability Recommendation

This application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The labels have adequate information as required. The Office of Compliance has issued an "Acceptable" overall recommendation for all facilities. The submission of updated drug substance and drug product specifications, as agreed upon with the Applicant is satisfactory. Further the calibrated cup to be included with the 500ml bottle is adequate. Therefore, from the CMC perspective, this NDA is recommended for Approval with a 24 month expiry for the 500ml bottles and 18 month expiry for the unit dose cups, when stored under ambient conditions and further with the Phase 4 commitment discussed above and in section P. 2.5 below.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Chemistry Reviewer: Julia Pinto, Ph.D.
CMC Lead: Danae Christodoulou, Ph.D.
Project Manager: Dominic Chiaperino
Prasad Peri, Ph.D, Branch Chief,

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

/s/

JULIA C PINTO
12/23/2011

PRASAD PERI
12/23/2011
I concur



CHEMISTRY REVIEW



NDA 201194

VistaPharm, Inc.

Julia C. Pinto, Ph.D.
Office of New Drug Quality Assessment, Division III

Division of Anesthesia, Analgesia and Addiction Products

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Chemistry Review Data Sheet

Chemistry Review Sheet

1. NDA 201194
2. REVIEW #: 1
3. REVIEW DATE: October 1, 2010
4. REVIEWER: Julia C. Pinto, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

N/A

6. SUBMISSIONS BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original NDA

May 4, 2010

Amendment

May 24, 2010

Amendment

June 29, 2010

Amendment

September 7, 2010

Amendment

October 11, 2010

7. NAME AND ADDRESS OF APPLICANT:

Name: VistaPharma
Address: 7265 Ulmerton Road
Largo, Florida, 33771

Representative: John G. Lay, Director Regulatory Affairs
Telephone: 727-530-1633 (jlay@vistapharm.com)

8. Product Drug Code and Name:

- a) Proprietary Name: None
- b) Non-Proprietary Name (USAN): Oxycodone Hydrochloride Oral Solution
- c) Code name/#(ONDQA only):
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: Type 2
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: FD&C ACT 505(b)(2)

10. PHARMACOLOGICAL CATEGORY:

Treatment of moderate to severe pain where the use of an opioid analgesic is appropriate.

Chemistry Review Data Sheet

11. DOSAGE FORM: Oral Solution
12. STRENGTH/POTENCY: 5mg/5ml
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed
 Not a SPOTS product

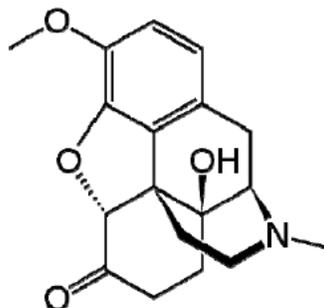
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

- Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-17-methyl-,hydrochloride,(5 α)-.
- 4,5 α -Epxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Molecular Formula: C₁₈H₂₁NO₄.HCl

CAS: 124-90-3

MW: 351.82



17. RELATED/SUPPORTED DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	Code ¹	Status	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	7			Since the manufacturing process is revised and referenced to DMF (b) (4), and the drug substance used in the manufacture of the clinical and marketed batches of drug product is from DMF (b) (4), DMF (b) (4) was not reviewed.
	II			1	Inadequate	Nov 2010	Julia Pinto Rev #1

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	4			
	III		4			
	III		4			
	III		4			
	IV		1	Adequate	12/1/2010	J Pinto, Ph.D. Rev. #1

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

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5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	105754	Oxycodone HCl Oral Solution 5mg/5ml

18. Status

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Adequate	June 10, 2010	Office of Compliance
Pharm/Tox	Not Approved pending updated specification for (b) (4) Impurity	January 14, 2011	Elizabeth Bolan

Chemistry Review Data Sheet

Biopharm	NA		
LNC	NA		
Methods Validation	NA		
DMET/DDMAC			
EA	Categorical exclusion satisfactory	May 2010	J. Pinto
Microbiology	NA		

Executive Summary Section

The Chemistry Review for NDA 201194**The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

This application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The Office of Compliance has issued an "Acceptable" overall recommendation for all facilities involved in production of the product. Labels have some of the required information. However, several deficiencies are noted at the end of this review. Further, while the Applicant has agreed to (b) (4) in the drug substance to NMT (b) (4), a revised specification tables for the drug substance, has not been provided. Further, since the manufacture of the drug substance uses (b) (4) testing and specifications for heavy metals is to be part of the DS release testing. Therefore, from the CMC perspective, this NDA is recommended as "Approvable" pending submission of the updated drug substance specifications and resolution to the labeling deficiencies.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable-

No Post Approval commitments are required.

II. Summary of Chemistry Assessment**A. Description of Drug Substance and Drug Product:**

The drug substance used in this product is oxycodone hydrochloride and is referenced to DMF (b) (4). Under DMF (b) (4), the process to produce the drug substance, also produced an (b) (4). The (b) (4) is an (b) (4) that is (b) (4) oxycodone. However, to limit the amount of (b) (4) that forms in the process, (b) (4) modified their process, under DMF (b) (4), to include an additional (b) (4). The new process and improved quality drug substance, having minimal (b) (4) present, is the subject of the second (b) (4) DMF (b) (4). Therefore, the drug substance used in the manufacture of the clinical and commercial batches of drug product is that obtained under DMF (b) (4). The drug substance specifications provided during the course of the review, reflected the higher limits of (b) (4), under DMF (b) (4). Updated specifications with (b) (4) controlled at NMT (b) (4) were requested of the Applicant. Further, testing and a specification for heavy metals, has also been requested as part of the release testing of the Drug Substance, since (b) (4) during manufacture of the DS. Approvability of this submission, is pending receipt of the updated DS specifications.

The drug product is manufactured as a 5mg/5ml oral red solution. The formulation includes sodium benzoate (b) (4), red colorant and raspberry flavoring. It will be packaged in two configurations, 5ml unit dose cups and 500ml HDPE bottle. A dosing device was not provided for in this original NDA submission. Upon discussions between the division and the

Executive Summary Section

Applicant, it was agreed to provide a calibrated cup to be included with the 500ml bottle. Submission of the specifications for the calibrated cup is pending.

Stability studies demonstrated that the product is stable, stored in both configurations at 25°C/60%RH or at 40C/75%RH. An expiry of 24 months for the 500ml bottles and 18 months for the unit dose cups, is granted.

B. Description of How the drug is intended to be used:

The proposed drug product is an immediate release oral solution containing 5mg/5ml of oxycodone HCl. It is intended for use in the treatment of moderate to severe pain where the use of an opioid analgesic is appropriate.

C. Basis for Approvability Recommendation

This application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The labels have adequate information as required. The Office of Compliance has issued an "Acceptable" overall recommendation for all facilities. However, submission of updated drug substance specifications, as agreed upon with the Applicant is pending, as is the submission of a calibrated cup for administration of the drug product from the 500ml bottle. Therefore, from the CMC perspective, this NDA is recommended for "Approvable Action" with a 24 month expiry for the 500ml bottles and 18 month expiry for the unit dose cups, when stored under ambient conditions.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Chemistry Reviewer: Julia Pinto, Ph.D.

Pharmaceutical Assessment Leader: Danae Christodoulou, Ph.D.

Project Manager: Dominic Chiapperino

Prasad Peri, Ph.D, Acting Branch Chief,

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/s/

JULIA C PINTO
01/21/2011

PRASAD PERI
01/21/2011
I concur

Initial Quality Assessment
Division of Pre-Marketing Assessment III, Branch VII
Office of New Drug Quality Assessment
Division of Anesthesia, Analgesia and Addiction Products

OND Division: Anesthesia, Analgesia and Addiction
NDA: 201194
Chemical Classification 3S
Applicant: VistaPharm
Stamp date: May 4, 2010
PDUFA Date: March 4, 2011
Trademark: NA
Established Name: Oxycodone Oral Solution, USP
Dosage Form: Oral solution, 5 mg/5ml
Route of Administration: Oral
Indication: Treatment of moderate to severe pain where the use of an opioid analgesic is appropriate

Initial Quality Assessment: Julia Pinto, Ph.D.

	YES	NO
ONDQA Fileability:	<u>√</u>	___
Comments for 74-Day Letter:	<u>√</u>	___

Summary, Critical Issues and Comments

A. Summary

The application is filed as a 505(b)(2), non-priority NDA with 10-month review clock for Oxycodone Oral Solution. This product falls under the Drug Efficacy Study Implementation (DESI). The Applicant is seeking to remove Oxycodone oral solution 5mg/5ml from the DESI list with approval of this NDA. The drug substance, oxycodone, is supplied by (b)(4) under DMFs (b)(4). The manufacturing process, by (b)(4) was modified, during the development program of the drug product, under this NDA. Therefore reference throughout this submission, is to the oxycodone drug substance obtained from (b)(4), under both DMFs. The manufacture of oxycodone drug substance, under DMF (b)(4), was modified to control the amount of (b)(4) in the final product. Therefore, DMF (b)(4), with the modified manufacturing process, is referenced as the low level (b)(4) oxycodone and DMF (b)(4) is the medium level (b)(4) oxycodone. The amount of (b)(4) under DMF (b)(4) was (b)(4) and under DMF (b)(4) is less than (b)(4). The description of the drug substance, the manufacturing processes, controls, analytical methods, and specifications of the API are referenced to both of these DMFs. LOAs are provided.

For the Drug Product, the excipients used in the composition are compendial with the exception of the raspberry flavoring, which due to the large amount used in the composition, and considering that is not GRAS under CFR regulations, should be reviewed. The Applicant has provided data of relative bioavailability studies and is not requesting a biowaiver.

The container closure systems are 5ml unit dose cups and 500ml HDPE bottles. Requested expiry is 18 months for the unit dose and 24 months for the HDPE bottles.

B. Drug Substance

Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight

Chemical names:

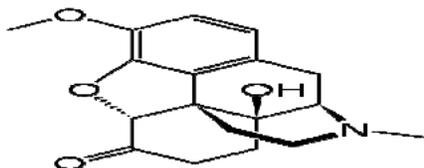
•Morphinan-6-one, 4,5-epoxy-14-hydroxy-3,17-methyl-hydrochloride, (5a)-

- Molecular Formula: C₁₈H₂₁NO₄.HCl

CAS: 76-42-6 and 124-90-3

MW: 351.82

Figure 1. Structure of oxycodone . HCl



Potential Impurities and degradation products:

The impurities listed in the table below are controlled by the HPLC methods which are referenced to DMF (b)(4) and a structural alert for mutagenicity and is controlled at NMI (b)(4) according to the drug substance proposed specifications, in Table 2, to be consistent with the USP monograph. However, the specification set by (b)(4) is a (b)(4) control and is not in agreement with what is proposed by the Applicant.

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Container Closure:

The applicant provided the packaging components of the HDPE bottles, cups and closures, and references to their corresponding DMFs. Letters of Authorization to the packaging DMFs have been included in the NDA. The applicant stated that the proposed container/closure system complies with USP<661> and <671>. Testing results according to these USP methods are provided. Further, the Applicant states that the resin materials used for the container closure systems have been verified according to 21 CFR 177.1520 and meet all intended use for food contact applications. Therefore, the Applicant is requesting to be exempt from leachable/extractable study requirements.

Stability:

Stability testing of the two fills (5ml and 500 ml) across four batches is performed under standard ICH conditions at 25°C/60% RH, and 40°C/75% RH. Stability protocols and post-approval stability commitment were provided in the NDA. The proposed expiration dating is 18 months for the 5ml unit dose cup and 24 months for the 500ml HDPE bottle. The 500 ml configuration has completed a 6-month accelerated study and 18 months at room temperature. The 5ml unit dose configuration has completed a 6-month accelerated study and a 12 month room temperature study. Further, data from an in-use study of two batches of open bottles is provided.

Labeling

Labeling information of the container labels and packaging insert should be assessed with respect to CMC related information.

C. Critical issues for review and recommendation

During assessment of the CMC information provided in this NDA, the primary reviewer should consider addressing issues identified above and other related ones, summarized here, for their impact on drug product quality and performance throughout the shelf-life:

1. Limits of impurities and related substances in the drug substance as per ICH Q3A(R), in consultation with the Toxicology Division and limits of residual solvents for compliance with ICH Q3C.
2. The suitability of the compendial specifications of excipients for drug product manufacturability, quality and performance should be assessed, in particular, supplier and specifications of raspberry flavor.
3. Details of the manufacturing process of the drug product, e.g.: in-process controls, hold times of the compounded solution and manufacturing conditions
4. Drug product specifications, e.g., impurity/degradant limits as per ICH Q3B(R), (b) (4) limits as a structural alert, and unidentified impurity limits, in consultation with the Toxicology Division.
5. The suitability of the HPLC method for related substances to detect (b) (4) and unidentified impurities.
6. No photostability testing of the drug product has been reported and should be requested.
7. The applicant requested a “biowaiver” for “human clinical efficacy and safety trials other than the relative bioavailability study performed” as amended on May 28.
8. Labeling in Structured Product Labeling (SPL) format has not been provided and should be requested.

D. **Comments for 74-day Letter:**

1. Provide a photostability study for the drug product, as per ICH Q1B.
2. Provide the packaging and release facility for the drug product.
3. Provide a retest period for the drug substance used in the manufacture of the drug product.
4. Provide a Letter of Authorization for access to the DMF for raspberry flavoring.
5. Provide unit dose cup and HDPE bottle samples with associated dosing cup.

E. **Recommendation for fileability:** The NDA is fileable based on pre-NDA agreements and 11 release batches and 4 stability batches with 12 to 18-month long term/6-month accelerated stability data for drug product packaged in the two proposed commercial presentations. The NDA is suitable for evaluation and assessment based on FDA and ICH guidelines for submitting CMC information for New Drug Applications.

Recommendation for Team Review: The NDA is not recommended for a team review.

Consults:

1. Toxicology

2. Biopharmaceutics, ONDQA (submitted 6/21/10; Angelica Dorantes was notified)

Microbiology consult was not deemed necessary. However, it may be initiated by the primary reviewer after evaluation of the firm's specifications, and supporting data.

Julia Pinto, Ph.D.
Primary CMC Reviewer

6/21/2010
Date

Prasad Peri, Ph.D.
Branch II Chief (Acting), ONDQA

6/21/2010
Date

NDA Number: 201194

Supplement Number and Type: 3S

Established/Proper Name:

Oxycodone oral solution

Applicant: VistaPharm

Letter Date: 05/04/2010

Stamp Date: 05/04/2010

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		(M3)
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		(b) (4), DMF (b) (4)
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		Packaging Facility has not been identified

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		
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* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		Referenced to DMF [REDACTED] (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Referenced to DMF [REDACTED] (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Referenced to DMF [REDACTED] (b) (4)
15.	Does the section contain controls for the DS?	X		Specifications included in the NDA
16.	Has stability data and analysis been provided for the drug substance?	x		Referenced to DMF [REDACTED] (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?		X	
23.	Have any biowaivers been requested?	X		
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	NA (Solution Oral Dosage Form)

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	x		Based on pre-NDA agreements and sufficient data
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		x	

{See appended electronic signature page}

Name of

PAL: Danae Christodoulou, Ph.D.

Primary CMC Reviewer: Julia Pinto, Ph.D. 6/21/10

Division of Pre-Marketing Assessment I

Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Name of

Branch Chief (Acting): Prasad Peri, Ph.D.

Division of Pre-Marketing Assessment I

Office of New Drug Quality Assessment

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-201194	----- ORIG-1	----- VISTAPHARM INC	----- OXYCODONE HCL SOLUTION

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

/s/

JULIA C PINTO
07/08/2010

PRASAD PERI
07/08/2010
I concur