CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206627Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

Date October 16, 2014

From Juandria Williams, PhD
Team Leader (Acting)
New Drug Manufacturing Assessment Branch
Division of Good Manufacturing Practice Assessment
Office of Manufacturing and Product Quality

Subject Non-concurrence with the (b) (4) Withhold Recommendation for NDA 206627, Hysingla ER (hydrocodone bitartrate), 20, 30, 40, 60 80, 100, and 120 mg

Thru Mahesh Ramanadham, PharmD/MBA, RPH; Branch Chief, NDMAB, OMPQ/DGMPA

To Julia Pinto, PhD; Branch Chief, Branch VIII, ONDQA/Division III

Applicant: Purdue Pharma, LP
One Stamford Forum
201 Tresser Blvd.
Stamford, CT 06901

Establishment: (b) (4)

The Division of Good Manufacturing Practice Assessment (DGMPA) has completed a review of an inspection package covering a pre-approval inspection (PAI) and GMP inspection conducted by (b) (4) investigators from (b) (4) at (b) (4). DGMPA has also reviewed the firm's written response (dated (b) (4) to the FDA Form-483 observations. This inspection was initiated by (b) (4) to provide pre-approval coverage of NDA 206627. (b) (4) is named in the application as the site for manufacturing and release testing of the API hydrocodone bitartrate. Purdue Pharma LP submitted NDA 206627 April 28, 2014 to provide for the manufacturing and commercial distribution of Hysingla (hydrocodone bitartrate) ER, 20, 30, 40, 60, 80, 100, and 120 mg.

The (b) (4) recommended withholding approval of NDA 206627 due to an incomplete cleaning validation of the Hydrocodone API (b) (4). DGMPA does not concur with (b) (4) withhold recommendation.

The firm provided a cleaning process development and validation summary report from September 2012 (MFG VAL 4.6.11 RPT), to the investigator, which documents the development and the then-current state of validation of the cleaning processes for (b) (4). The report includes data for a cleaning study on one batch of hydrocodone bitartrate which was last manufactured in 2012. The data does suggest that they are able to clean the (b) (4) and meet their pre-determined residual threshold. The firm has since been unable to manufacture hydrocodone bitartrate due to DEA restrictions, and has therefore been unable to perform additional equipment cleaning iterations for hydrocodone bitartrate. DGMPA believes that the

data from the 2012 cleaning batch does demonstrate that the firm can clean the (b) (4) such that the potential risk to patient safety from cross-contamination of products in the shared equipment is mitigated. Additionally, the firm does commit to update their summary reports for the development, qualification, verification, and/or validation of cleaning procedures for hydrocodone bitartrate and its intermediates for (b) (4), among other (b) (4), by the end of 2014.

CDER/OC/OMPQ/DGMPA Recommendation:

Based on the above assessment of the inspection findings and the firm's response to Form 483 observations, DGMPA does not concur with the (b) (4) recommendation to withhold approval of NDA 206627, Hysingla ER (hydrocodone bitartrate), 20, 30, 40, 60 80, 100, and 120 mg DGMPA recommends that corrective actions to the Form 483 should be verified on a follow up inspection.

If you have any questions, please contact me at (301) 796-4916 or by email at juandria.williams@fda.hhs.gov

Juandria Williams, PhD
Team Leader (Acting)

cc:

(b) (4) Pre-Approval Manager (PAM)
CMS case #: (b) (4)

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/s/

JUANDRIA WILLIAMS
10/16/2014

MAHESH R RAMANADHAM
10/16/2014

NDA 206-627

Hydrocodone Bitartrate
Q24H Film-Coated Tablets (HYD)
(Hydrocodone Bitartrate)

Purdue Pharma L.P.

Xiaobin Shen, Ph.D.
for
Division of Anesthesia, Analgesia and Addiction Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 206-627

2. REVIEW #: 1

3. REVIEW DATE: 31-Jul-2014

4. REVIEWER: Xiaobin Shen, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NA	NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	28-Apr-2014
Amendment 0002	06-May-2014
Amendment 0011	16-Jul-2014
Amendment 0012	17-Jul-2014
Amendment 0013	18-Jul-2014
Amendment 0014	18-Jul-2014
Amendment 0016	24-Jul-2014
Amendment 0017	28-Jul-2014
Amendment 0018	30-Jul-2014

Other amendments dated older than the last listed do not have CMC related information for review.

7. NAME & ADDRESS OF APPLICANT:

Name: Purdue Pharma L.P.

Chemistry Review Data Sheet

Address:	One Stamford Forum, 201 Tresser Blvd., Stamford, CT 06901
Representative (Agent):	Edward Liao, Pharm.D. Director of US Regulatory Affair One Stamford Forum, 201 Tresser Blvd., Stamford, CT 06901
Telephone:	203-588-7558
Fax:	203-588-6229
Email:	Edward.liao@pharma.com

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Hysingla ER
b) Non-Proprietary Name (USAN): Hydrocodone Bitartrate
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: NDA 505(b)(2)

10. PHARMACOL. CATEGORY: Opioid agonist

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 20, 30, 40, 60, 80, 100, and 120 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

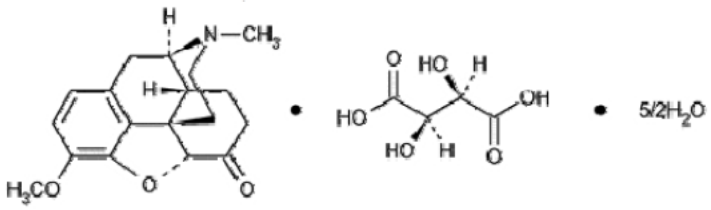
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

Chemical name: 4,5α-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)
United States Adopted Name (USAN): Hydrocodone Bitartrate
Compendial name: Hydrocodone Bitartrate
Chemical structure:



Molecular Formula: $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2½H_2O$
Molecular Weight: 494.49

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Hydrocodone bitartrate	1	Adequate	16-Jul-2014	NA
		(b) (4)		4			
				4			
				4			
				4			
				4			

		(b) (4)				
(b) (4)			4			
			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
NA	NA	NA

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	31-Jul-2014	Xiaobin Shen
Pharm/Tox	Pending	31-Jul-2014	Dr. Elizabeth Bolan
Biopharm	Pending	31-Jul-2014	Dr. Akm Khairuzzaman
Methods Validation	Not needed	07-Jun-2014	Xiaobin Shen
EA	Adequate	07-Jun-2014	Xiaobin Shen
Microbiology	Pending	31-Jul-2014	Dr. John Metcalfe

The Chemistry Review for NDA 206-627

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval, pending a satisfactory EES status.

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

NA.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

Hydrocodone bitartrate drug substance exists as fine, white crystals or crystalline powder. It is soluble in water. The NDA contains no other physicochemical properties of the drug substance. The NDA does not contain pharmacological related information about the drug substance either, it is filed in reference to the FDA approved Vicoprofen® tablet product. Support for the drug substance is completely referenced to DMF (b) (4).

The hydrocodone bitartrate drug substance is manufactured by (b) (4) per DMF (b) (4). The DMF has been last reviewed by this reviewer on 16-Jul-2014 and deemed adequate. There has been no change to the DMF since that review. The drug substance manufacturer site EES status is pending.

Specifications for hydrocodone bitartrate drug substance include both USP and ICH requirements. Collectively they include appearance, identification, specific rotation, pH, assay, impurities, loss on drying, residue on ignition, residual solvents and particle size distribution. The drug substance is packaged in (b) (4) bags inside a (b) (4) drum. The drug substance stability data was referenced to DMF (b) (4), which is adequate to support its use in the NDA. It has a retest date of (b) (4) months.

The drug product is available as 20, 30, 40, 60, 80, 100 and 120 mg strength (b) (4) The different strengths is differentiated by the film coating color as well as over print of "HYD 20", where 20 stands for the strength of 20 mg and changes according to the specific product strength.

The differentiation is important because all strengths have the same tablet shape, weight and size. The common excipients include Hydroxypropyl Cellulose, Macrogol/PEG 3350, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Oxide (PEO), Polysorbate 80, Polyvinyl Alcohol, Talc, Titanium Dioxide, and Black Ink. Each strength also contains its unique film coating colorants. All excipients are of compendial grades. The magnesium stearate is (b) (4) PEO is used at quantities (b) (4) than used in already approved products. The safety of this excipient is evaluated by the pharm/tox reviewer Dr. Elizabeth Bolan. The tablets are packaged in (b) (4) cc white oblong HDPE bottles at 60 count and closed with a child-resistant closure. Each bottle also contains two oxygen absorbers. The drug product is manufactured and packaged by applicant's site located in (b) (4) The drug product manufacturing and testing sites have satisfactory EES status.

The drug product specifications include appearance, identification, assay, related substances, content uniformity, and dissolution. Microbial limit testing is not included in either release or stability testing. Microbiologist, Dr. John Metcalfe, has been working with the applicant to ensure that adequate control is in place for the final commercial drug product. The drug product primary stability studies were conducted on 3 batches for each strength and packaging configuration combinations. Up to 18 months of stability data is provided for the product stored under long term (25°C/60% RH) storage conditions and six months of stability data is provided for the storage under accelerated conditions (40°C/75% RH). All tested quality attributes (description, assay, degradation products, and dissolution) results remained relatively stable and showed no trend during the time periods studied for all product strength/packaging configuration combinations and under all storage conditions. Overall, the provided stability data supports the applicant's proposed 24 month product expiry.

B. Description of How the Drug Product is Intended to be Used

The product is indicated for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. It is proposed to be administered starting at 20 mg every 24 hours and titrated up as necessary.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provided acceptable information on the chemistry, manufacturing, and controls of the hydrocodone bitartrate extended release tablets. The product is recommended for approval based on the following:

- The drug substance and product specifications provide adequate controls;
- The drug product excipients are of USP/NF grade;
- The drug product container closure systems are acceptable for pharmaceutical use.

- Both drug substance and drug product are stable in the studied stability period and support the currently proposed expiry of 24 months for the drug product.

D. Risk Assessment

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
		H, M, or L		Acceptable or Not acceptable	

To be completed in the amendment review.

III. Administrative

A. Reviewer's Signature

Review is digitally signed off in DARRTS.

B. Endorsement Block

Chemist Name/Date: See digital sign off at end of document
Chemistry Branch Chief Name/Date: See digital sign off at end of document

C. CC Block

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/s/

XIAOBIN SHEN
07/31/2014
The NDA is recommended for approval from CMC perspective pending satisfactory a EES status.

JULIA C PINTO
08/01/2014

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 206627
2. DATES AND GOALS:

Letter Date: April 18, 2014	Submission Received Date : April 18, 2014
PDUFA Goal Date: October 18, 2014	Granted Priority Review

3. PRODUCT PROPERTIES:

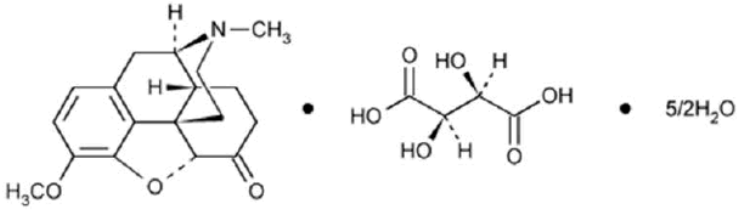
Trade or Proprietary Name:	Hysingla ER
Established or Non-Proprietary Name (USAN):	Hydrocodone Bitartrate ER Tablets
Dosage Form:	Film-Coated Q24h Tablets
Route of Administration	Oral
Strength/Potency	20, 30, 40, 60, 80, 100, 120mg
Rx/OTC Dispensed:	Rx

INDICATION:

Hysingla ER (HYD) is a once daily, extended release tablet for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

DRUG SUBSTANCE STRUCTURAL FORMULA:

Structural Formula



Hydrocodone Bitartrate MW: 494.50

4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)

4. **NAME OF APPLICANT** (as indicated on Form 356h):

Purdue Pharma, LP
One Stamford Forum
201 Tressor Blvd
Stamford, CT 06901

5. SUBMISSION PROPERTIES:

Review Priority:	Priority Review
Submission Classification (Chemical Classification Code):	
Application Type:	505(b)(2)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DAAAP

6. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		EES entered May 21, 2014 by Luz Riviera
Pharmacology/Toxicology		X	
Methods Validation		X	
Environmental Assessment		X	
CDRH		X	
Other	X		Microbiology Consult Sent: April 28, 2014 John Metcalfe is the assigned Micro. Reviewer

Overall Filing Conclusions and Recommendations

Is the Product Quality Section of the application fileable from a CMC perspective? Yes **X** No
CMC Filing Issues: **None**

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? Yes X No
CMC Comments for 74-Day Letter:
1. (b) (4) 2. 3. 4. 5. Provide the analytical method description and validation for all in-house methods used to qualify the API prior to use in the manufacture of the drug product.

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes X No
Biopharmaceutics Filing Issues: See Filing Review by Akm Khairuzzaman, Ph.D.
Biopharmaceutics Filing Review was entered into DARRTs separately from this CMC filing review, by A. Khairuzzaman/T.Ghosh.

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? Yes X No
Biopharmaceutics Comments for 74-Day Letter:
See Biopharm Filing Review by A. Khairuzzaman in DARRTs.

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?
Yes X No
Microbiology Filing Issues: None
See Filing Review in DARRTs by John Metcalfe, Ph.D.

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain

Is a team review recommended?	Yes	No X
Suggested expertise for team:		

Summary of Critical Issues and Complexities

Initial Quality Assessment

Hydrocodone bitartrate is formulated as an ER film-coated, abuse deterrent tablet designed to provide sustained analgesia support for 24 hours. This NDA is a 505b2 using Vicoprofen® as the reference product. It has been granted priority status since it is the first hydrocodone drug product where Hydrocodone is the single API in an abuse deterrent formulation.
The tablet strengths are 20mg, 30mg, 40mg, 60mg 80mg, 100mg and 120mg. The proposed color coating and description for each is below. The tablets are stored in HDPE bottles with 2 (b) (4) for moisture control.

Hydrocodone Bitartrate q24h Film Coated Tablets with the following descriptions:

20 mg:	Round green tablet with "HYD" and "20" printed in black ink on one side and no printing on the other side
30 mg:	Round yellow tablet with "HYD" and "30" printed in black ink on one side and no printing on the other side
40 mg:	Round gray tablet with "HYD" and "40" printed in black ink on one side and no printing on the other side
60 mg:	Round beige tablet with "HYD" and "60" printed in black ink on one side and no printing on the other side
80 mg:	Round pink tablet with "HYD" and "80" printed in black ink on one side and no printing on the other side
100 mg:	Round blue tablet with "HYD" and "100" printed in black ink on one side and no printing on the other side
120 mg:	Round white tablet with "HYD" and "120" printed in black ink on one side and no printing on the other side

FILING REVIEW CHECKLIST

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*				
*	**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.**			
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
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

	Parameter	Yes	No	Comment
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • 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		Manufacturing facilities are listed at the end of the Review.
8.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • 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		Manufacturing facilities are listed at the end of the Review.

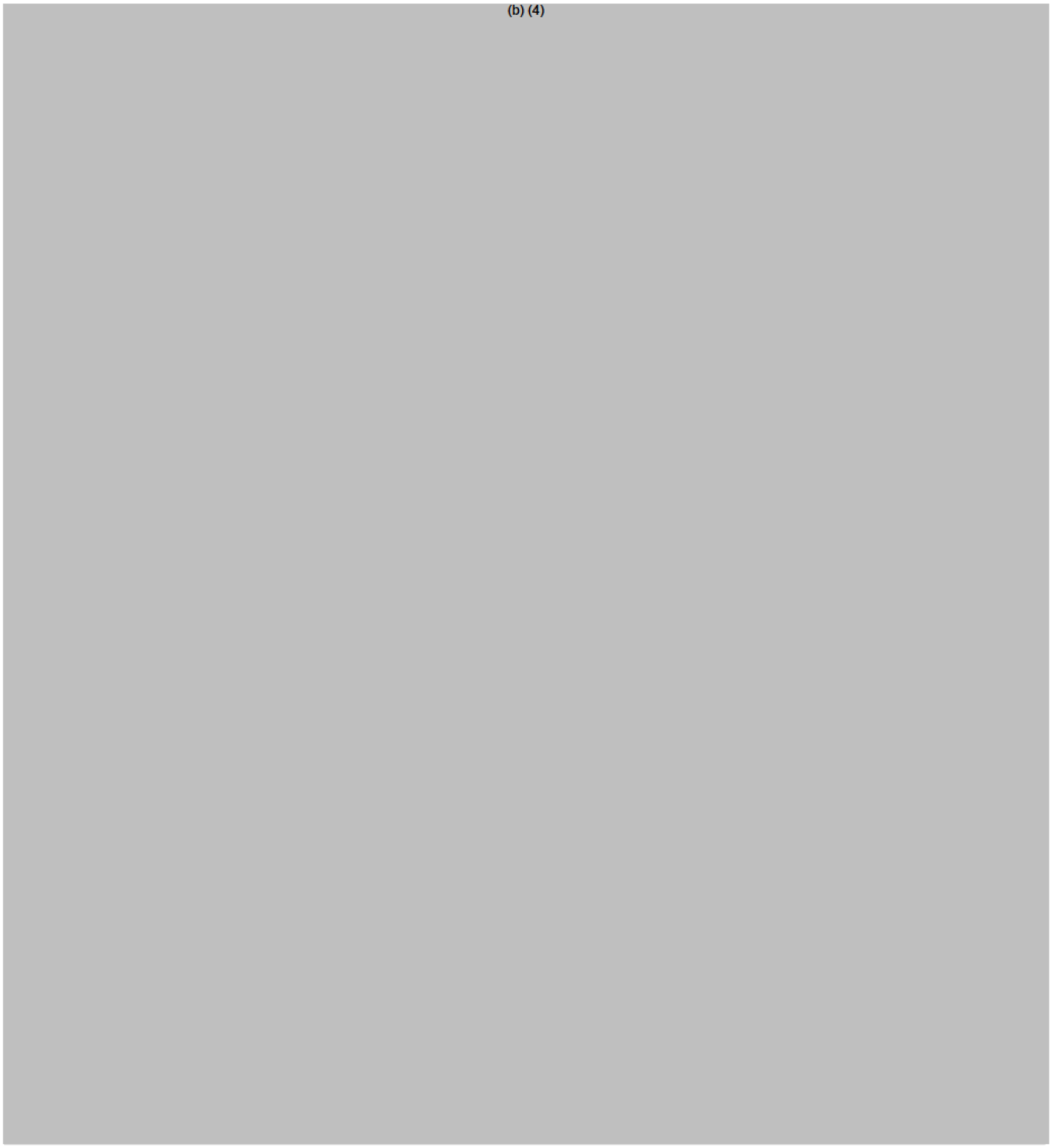
	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI 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		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment or claim of 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 (b) (4)
13	Does the section contain identification and controls of critical steps and intermediates of the DS?		x	Referenced to DMF (b) (4)
14	Does the section contain information regarding the characterization of the DS?		x	Referenced to DMF (b) (4)
15	Does the section contain controls for the DS?	x		
16	Has stability data and analysis been provided for the drug substance?		x	Referenced to DMF (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	

Hydrocodone- API Specifications

(b) (4)



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	

Drug Product Composition:

(b) (4)

Drug Product Release and Stability Specifications for the 20mg tablets (exemplary) are shown below.

Bulk Tablets

TEST	*SPECIFICATION/LIMIT*	*METHOD NUMBER*
Appearance	(b) (4)	Visual Examination
Identification (UV)		TM-0154
Identification (HPLC)		TM-0056
Assay		TM-0056
Uniformity of Dosage Units		TM-0056
Dissolution - Extended Release		TM-0053
Degradation Products (b) (4)		TM-0055

Notes:
(b) (4)

Stability

TEST	*SPECIFICATION/LIMIT*	*METHOD NUMBER*
Appearance	(b) (4)	Visual Examination
Assay		TM-0056
Dissolution - Extended Release		TM-0053
Degradation Products		TM-0055
(b) (4)		

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		.

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		LOAs for all pertinent DMFs are provided.

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		

Manufacturing Facilities for Drug Substance and Drug Product:

The Manufacturer for the Hydrocodone Bitartrate API is:

Facility Name and Address	Site Registration No.	Manufacture	Analytical Testing	
			Release	Stability
(b) (4)				

Drug Product Manufacturing Sites

Table 1. Sites of Drug Product Manufacturing, Packaging and Control

Facility Name and Address	Site Registration No.	Manufacture and Package	Analytical (R=Release, S=Stability, M=Micro) DPC=Drug Product Component DP=Drug Product PM=Packaging Materials				
			DPC		DP		PM
			R	M	R	S	R
(b) (4)							

See appended electronic signature page}
NAME : *Julia Pinto, Ph.D.*
CMC-Lead
Division III
Office of New Drug Quality Assessment

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
06/06/2014