

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202880Orig1s000**

**CHEMISTRY REVIEW(S)**

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

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**DATE:** Sept 24, 2013

**FROM:** Yong Hu, Ph.D.

**SUBJECT:** Addendum #2 to CMC Review #1 of NDA 202880 for  
Zohydro ER (hydrocodone bitartrate) extended-release capsule  
Applicant: Zogenix, Inc

**TO:** NDA 202880 file

In the amendment submitted on Sept 24, 2013, the applicant requests that the (b) (4)-count bottle configuration be withdrawn from marketing consideration. The applicant states that it only intends to market the 100-count bottles.

The applicant has submitted the updated draft labeling, where the information about the (b) (4) ct bottles has been removed from the “How Supplied/Storage and Handling” section (see below).

**16 HOW SUPPLIED/STORAGE AND HANDLING**

Zohydro ER extended-release capsules are supplied in (b) (4) 100-count bottles with a child-resistant closure as follows:

Strength	Capsule Color(s)	Capsule Text	NDC Number
10 mg	White opaque	“Zogenix 10 mg” in black ink	(b) (4) 43376-210-10 100 ct bottles
15 mg	Light green and white opaque	“Zogenix 15 mg” in black ink	(b) (4) 43376-215-10 100 ct bottles
20 mg	Light green opaque	“Zogenix 20 mg” in black ink	(b) (4)

			(b) (4) 43376-220-10 100 ct bottles
30 mg	Dark blue and white opaque	“Zogenix 30 mg” in black ink	(b) (4) 43376-230-10 100 ct bottles
40 mg	Dark brown and white opaque	“Zogenix 40 mg ” in black ink	(b) (4) 43376-240-10 100 ct bottles
50 mg	Dark brown opaque	“Zogenix 50 mg ” in black ink	(b) (4) 43376-250-10 100 ct bottles

The information amendment is acceptable.

It should be noted that the stability data for both the 100-ct and the (b) (4)-ct bottles have been reviewed in the CMC review #1. If the applicant chooses to market the (b) (4) ct bottles after the NDA approval, they can submit a post-approval supplement referencing the stability data submitted in the original NDA and including updated labeling and carton/container labels for the (b) (4) ct bottles.

**Recommendation:** All CMC issues have been satisfactorily addressed. This application can be approved.

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/s/  
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YONG HU  
09/24/2013

PRASAD PERI  
09/24/2013  
I concur

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

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**DATE:** Feb 6, 2013

**FROM:** Yong Hu, Ph.D.

**SUBJECT:** Addendum to CMC Review #1 of NDA 202880 for  
Zohydro ER (hydrocodone bitartrate) extended-release capsule  
Applicant: Zogenix, Inc

**TO:** NDA 202880 file

This is a follow up to CMC Review #1 for the purposes of indicating resolution of the issues that were the conditions of the *Approval* recommendation.

In the CMC review #1, this reviewer's recommendation was "Approval" pending Alkermes' (DMF (b) (4) holder) adequate response to the biopharmaceutics comment in the Biopharmaceutics Review #1, dated 1/2/2013 and the applicant's withdrawal of the NDA's reference to (b) (4) drug substance DMF (b) (4)

Dr. Minerva Hughes, Biopharmaceutics reviewer, indicates in her review dated 1/24/2013, that "DMF Amendments 13 and 14 include the firm's response to the Biopharmaceutics comments (4 Jan 2013 deficiency letter) on the coating weight range. The firm (b) (4) their initially proposed limits to align with FDA's recommendation not to exceed a tolerance of (b) (4) for the release controlling polymer. The MBR for the sustained release beads was appropriately updated." She concludes that the DMF (b) (4) is adequate.

In the cover letter of the amendment, dated 1/25/2013, to NDA 202880, Zogenix states that "Zogenix hereby withdraws (b) (4) (b) (4) as the API manufacturer for the drug substance (Hydrocodone Bitartrate USP as described in (b) (4) DMF (b) (4) in the manufacture of Zohydro ER drug product as described in Zogenix NDA 202880. Any references to (b) (4) in this NDA are for historical support of the Zohydro ER (hydrocodone bitartrate) Extended-Release Capsules drug product approval." An updated FDA Form 356h has been included with the removal of (b) (4) in the Establishment Information. The NDA Section 2.3 Quality Overall Summary Introduction also includes the same statement above in support of the withdrawal of reference to DMF (b) (4)

**Recommendation:** All CMC issues have been satisfactorily addressed. This application can be approved.

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/s/  
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YONG HU  
02/06/2013

PRASAD PERI  
02/06/2013  
I concur

**NDA 202880**

**Zohydro ER  
(Hydrocodone Bitartrate) Extended Release Capsule**

**Zogenix, Inc.**

**Yong Hu, Ph.D.**

**Division of New Drug Quality Assessment III  
Office of New Drug Quality Assessment**

**For**

**Division of Anesthesia, Analgesia, and Addiction Products**

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# Chemistry Review Data Sheet

1. NDA: 202880
2. REVIEW #: 1
3. REVIEW DATE: 1/14/2013
4. REVIEWER: Yong Hu, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

N/A

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original submission

Quality/stability information amendment

Labeling/MedGuide Draft

Quality/stability information amendment

Quality/Response to CMC information request

Quality/Addition of testing sites

Document Date

5/1/2012

8/31/2012

11/4/2012

11/21/2012

12/28/2012

1/11/2013

7. NAME & ADDRESS OF APPLICANT:

Name:

Zogenix, Inc

Address:

5858 Horton Street, Suite 455  
Emeryville, CA 94608

Representative:

Nancy Yee, Director, Regulatory Affairs

Telephone:

510-550-8331

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Zohydro ER

## Chemistry Review Data Sheet

- b) Non-Proprietary Name (USAN): Hydrocodone bitartrate extended-release capsule  
c) Code Name/# (ONDC only): ELN154088  
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION:

505 b(2); The reference drug is Vicoprofen tablet (7.5 mg hydrocodone bitartrate / 200mg ibuprofen). Note that, unlike the reference drug, this NDA is for a single-entity hydrocodone product.

## 10. PHARMACOL. CATEGORY:

Analgesic.

## 11. DOSAGE FORM:

Extended-release capsule.

## 12. STRENGTH/POTENCY:

10, 15, 20, 30, 40, and 50 mg

## 13. ROUTE OF ADMINISTRATION:

Oral

14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

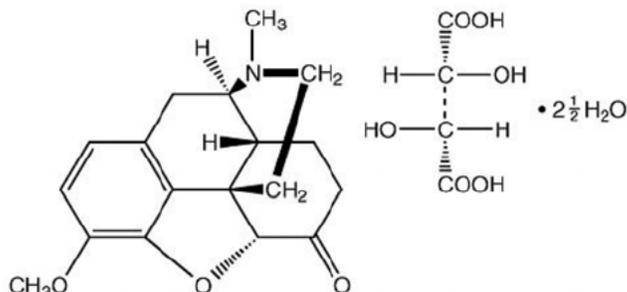
Not a SPOTS product

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

Morphinan-6-one, 4,5-epoxy-3-methoxy-17-methyl-,(5 $\alpha$ )-, [R(R\*,R\*)]-2,3-dihydroxybutanedioate (1:1), hydrate (2:5);

4,5 $\alpha$ -Epoxy-3-methoxy-17-methyl-morphinan-6-one tartrate (1:1), hydrate (2:5)

## Chemistry Review Data Sheet


 $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2} H_2O$ 

MW = 494.50

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Hydrocodone bitartrate API	1	Inadequate	9/27/2012	The FDA has notified the applicant that (b) (4) is <u>not</u> an acceptable supplier of the drug substance. The applicant acknowledged the receipt of the notification on 12/28/2013. In addition, the drug product manufacturer Alkermes commits to not using the (b) (4) drug substance in the manufacturing of the drug product via a response on 12/20/2012 to the CMC deficiency letter for the DMF (b) (4). The applicant will be asked to withdraw the reference to the DMF (b) (4).
(b) (4)	II	(b) (4)	Hydrocodone bitartrate API	1	Adequate	11/27/2012	
(b) (4)	II	Alkermes	Hydrocodone bitartrate extended-release capsules	1	Adequate pending the holder's response to Biopharm comment	1/2/2012 (Biopharm review #1) 1/4/2012 (CMC review #1)	

<sup>1</sup> Action codes for DMF Table:

Chemistry Review Data Sheet

- 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")

<sup>2</sup> 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	65111	Zogenix's IND

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not requested.		
EES	Acceptable. See Attachment II.	9/21/2012	M. Stock
Pharm/Tox	The impurity (b) (4) in the (b) (4) drug substance is not qualified for the specification limit of (b) (4) %; The (b) (4) % specification limit for (b) (4) in the drug product is qualified.	Email communications (1/7/2013 for (b) (4) see Attachment I)	Dr. Elizabeth Bolan
Biopharm	The biowaiver request for the 15 mg is acceptable.	Oral communication. Biopharm review pending.	Dr. Minerva Hughes
LNC	Not requested.		
Methods Validation	Not requested. Oral product. No novel analytical procedures.		
OPDRA	Not requested.		
EA	Acceptable.	1/9/2013	Dr. Yong Hu
Microbiology	Recommendation provided for the drug product DMF (b) (4) See DMF review.		Dr. Bryan Riley

# The Chemistry Review for NDA 202450

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The CMC recommendation is “Approval” pending Alkermes’ (DMF (b) (4) holder) adequate response to the biopharmaceutics comment in the Biopharmaceutics Review #1, dated 1/2/2013 and the applicant’s withdrawal of the NDA’s reference to (b) (4) drug substance DMF (b) (4)

It should be noted that the applicant proposes to use the hydrocodone bitartrate drug substance sourced from both (b) (4) and (b) (4) in the manufacturing of the drug product. However, only (b) (4) sourced drug substance is acceptable. The applicant has acknowledged the FDA’s notice that (b) (4) is not an acceptable drug substance supplier and the drug product manufacturer Alkermes (DMF (b) (4) holder) has committed to not using the drug substance from (b) (4) in its response to a deficiency letter. The applicant should further withdraw the reference to the (b) (4) DMF (b) (4) and update the manufacturers information.

An addendum will be made to this review with the final “Approval” recommendation once the above two issues are resolved.

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

None.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

This NDA references the (b) (4) DMF (b) (4) and (b) (4) DMF (b) (4) for the drug substance, and the Alkermes DMF (b) (4) for the drug product. Refer to the corresponding DMF reviews for more specific information as this summary can not include any confidential information from the DMFs.

The drug substance is hydrocodone bitartrate USP and the drug product is hydrocodone bitartrate extended-release capsule, 10, 15, 20, 30, 40, and 50 mg. Unlike the currently-approved hydrocodone products, which are all combination drug products (e.g. hydrocodone/acetaminophen and hydrocodone/ibuprofen), this NDA proposes a single-entity hydrocodone product. The DAAAP Division has determined that, as a single entity drug product, the maximum daily dose of hydrocodone bitartrate would be up to 3 g, much higher than those from the combination drug products.

## Executive Summary Section

The applicant proposed to use both (b) (4) and (b) (4) sourced drug substance for the drug product. The (b) (4) DMF (b) (4) has been referenced to support some approved ANDAs (combination drug products). However, it is not adequate to support this single-entity NDA because it does not show adequate manufacturing capability and product specification to control the impurities below the more stringent ICH qualification threshold for a drug product with > 2 g total daily dose. Therefore, (b) (4) is not an acceptable supplier for the drug substance. The applicant has acknowledged receipt of the FDA notification on this matter. The drug product manufacturer Alkermes has committed to not using the (b) (4) drug substance in the manufacturing of the drug product. The (b) (4) DMF is adequate. (b) (4) manufactures the drug substance in their (b) (4) or (b) (4) facilities, which have been deemed acceptable by the Office of Compliance.

Hydrocodone bitartrate extended-release (HC-ER) capsule (also named ELN154088 in some development documentation), is an extended-release capsule product using Alkermes' Spheroidal Oral Drug Absorption System (SODAS<sup>®</sup>) technology. With this technology the sugar spheres are initially coated with the drug substance and other suitable excipients to form immediate-release (IR) multiparticulates (beads). Sustained-release (SR) multiparticulates (beads) are then prepared by coating the IR beads with a rate-controlling polymer (ammonio methacrylate copolymer (b) (4) (b) (4) and other suitable excipients. The extended-release product is then achieved (b) (4) (20:80 w/w) followed by encapsulation to the desired product strength of 10, 15, 20, 30, 40, or 50 mg of hydrocodone bitartrate in hard gelatin capsules. It should be noted that all the capsule strengths (b) (4)

(b) (4). The excipients include sugar spheres, hypromellose, silicon dioxide, and talc in addition to the ammonio methacrylate copolymer (b) (4). The capsule shells contain titanium dioxide, FD&C Blue #1, FD&C Red #40, FDA Yellow iron oxide, FD&C Red #3, FDA Black iron oxide, FDA Red iron oxide, and gelatin. The drug product is manufactured by Alkermes Gaineville LLC (former Elan Holdings) in their Gaineville, Georgia facility, which has been deemed acceptable by the Office of Compliance.

One of the key elements in the Quality Target Product Profile (QTPP) is that the solid oral dosage form is taken every 12 hours for patient convenience, compliance and safety. The IR component is intended to provide rapid onset of analgesia with the SR component providing sustained action for a full 12 hour period. Refer to the DMF (b) (4) reviews (CMC and Biopharmaceutics) for the critical quality attributes and manufacturing controls for the drug product.

All the clinical trial supplies were manufactured with the (b) (4) drug substance. However, the (b) (4) drug substance has shown comparability to the (b) (4) drug substance in terms of the drug substance critical quality attributes and the performance of the drug product. Therefore, the use of (b) (4) drug substance in the commercial manufacturing is acceptable.

The applicant requests a biowaiver for the 15 mg strength as the 15 mg has never been evaluated in any PK or clinical study. The Biopharmaceutics reviewer and this CMC reviewer agree that

## Executive Summary Section

the biowaiver request is acceptable based on that 1) The 15 mg is (b) (4) and manufactured with the (b) (4); 2) The 15 mg is bracketed by the other strengths; 3) The 15 mg showed comparable batch analysis data to the other strengths.

The rate-controlling polymer ammonio methacrylate copolymer (b) (4) (b) (4) is soluble in alcohol, therefore, the extended-release characteristics of the product may be compromised in the presence of alcohol. Indeed, the applicant has observed increased drug release rates in ethanol (especially in 20% and 40 % concentrations) during the in-vitro dissolution studies. The applicant has conducted a PK study to investigate the effect of alcohol in-vivo. Based on the Clinical Pharmacology reviewer the PK study showed that 20% and 40% alcohol did not affect the AUCs of the drug but the 40% alcohol caused higher and variable Cmax. It is also this CMC reviewer's understanding that the alcohol effect observed in the PK study for this product is comparable to that observed for some other approved opioid products and much less than that observed for Palladone (hydromorphone hydrochloride) extended release capsule, which was withdrawn from the market. At the time of this review, the Clinical and Clin Pharm reviewers do not consider the observed in-vivo alcohol effect an approvability/safety issue. The alcohol effect is being addressed through labeling.

The drug product does not have any abuse-deterrent properties by design. The in-vitro abuse liability study shows that the drug can be extracted from the product using a variety of solvents including water, dilute acid and base and ethanol. Physical manipulation of the product (grinding, chewing, etc) breaks down the polymer coating and can facilitate the extraction of the drug substance from the product, as well as facilitating nasal insufflations of the contents.

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

The product is an opioid analgesic indicated for the management of moderate-to-severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

The product is taken every 12 hours. The proposed labeling states that "The capsules must be swallowed whole and must not be chewed, crushed or dissolved." and "Patients must not consume alcoholic beverages or prescription or non-prescription products containing alcohol while on Zohydro ER therapy."

The capsules are supplied in (b) (4) count or 100-count HDPE bottles with a child-resistant closure. The product is stored at 25° C (77° F); excursions permitted to 15°–30° C (59°–86° F). [See USP Controlled Room Temperature]. The proposed (b) (4) expiration dating period for the (b) (4) count and 24 months for the 100-count bottles are acceptable.

The product contains hydrocodone bitartrate, a Schedule II controlled substance with a high potential for abuse. The handling and distribution of the product will be subject to controlled substances regulations. Patients are advised to dispose of any unused capsules from a prescription as soon as they are no longer needed in accordance with local State guidelines and/or regulations.

## Executive Summary Section

**C. Basis for Approvability or Not-Approval Recommendation**

The CMC information is adequate to assure the identity, purity, strength and quality of the drug product. The manufacturing facilities are acceptable from cGMP perspective as determined by the Office of Compliance.

It is this reviewer's understanding that the NDA review team has not concluded that the risk of abuse and misuse of this product will be greater than that with other approved opioid products. The abuse liability of the product is being actively addressed through labeling and will be through REMS as well. Currently, the lack of abuse-deterrent features of the drug product, while recommended and desirable, is not considered an approvability issue by the Division and ONDQA. However, in the event that the Division determines that abuse liability becomes a significant concern that can not be addressed by the labeling and REMS, this reviewer would recommend that the NDA not be approved and the applicant reformulate the product to incorporate abuse-deterrent characteristics.

**III. Administrative****A. Reviewer's Signature**

See DARRTS.

**B. Endorsement Block**

See DARRTS.

**C. CC Block**

See DARRTS.

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/s/  
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YONG HU  
01/15/2013

PRASAD PERI  
01/15/2013  
I concur

**Initial Quality Assessment**  
**Office of New Drug Quality Assessment**  
**Division III, Branch VIII**  
**Division of Anesthesia, Analgesia and Addiction Products**

OND Division:	Anesthesia, Analgesia and Addiction	
NDA:	202880	
Chemical Classification	3S	
Applicant:	Zogenix Inc.	
Stamp date:	May 1, 2012	
PDUFA Date:	March 1, 2012	
Trademark:	Zohydro ER or CR	
Established Name:	Hydrocodone bitartrate, USP	
Dosage Form:	Extended-release capsules, 10, 15, 20, 30, 40, 50 mg	
Route of Administration:	Oral	
Indication:	Treatment of moderate to severe chronic pain	
CMC Lead:	Danae D. Christodoulou, Ph.D.	
	YES	NO
ONDQA Fileability:	<u>√</u>	_____
Comments for 74-Day Letter:	_____	<u>√</u>

## Summary, Critical Issues and Comments

### A. Summary

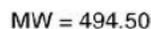
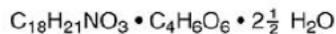
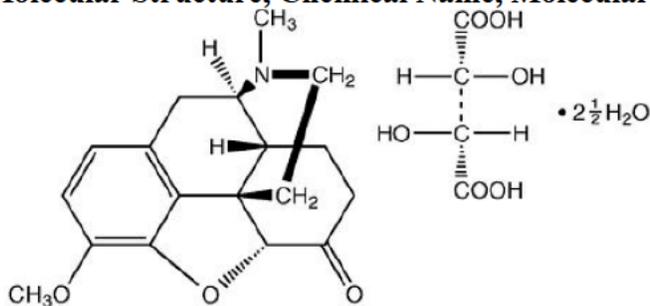
The application is submitted as a 505(b)(2), and aims to establish bioequivalence to the approved product Vicoprofen® tablet (7.5 mg hydrocodone bitartrate/200 mg ibuprofen), NDA 20-716, approved in September 23, 1997. The current NDA is supported by IND 65,111 originally submitted by Elan, and the drug product information is provided in a Drug Master File (DMF) (b)(4) currently owned by Alkermes. Pre-NDA meetings were held with the applicant, Zogenix, on November 17 (clinical) and 18 (CMC), 2011 and CMC agreements were reached with the applicant. Note that this is the first NDA submitted for the single entity hydrocodone bitartrate, a Schedule II narcotic. All approved hydrocodone drugs are Schedule III combination drugs with NSAIDs or other entities.

The proposed drug product will be available in six strengths: 10, 15, 20, 30, 40, 50 mg capsules and will be packaged in (b)(4) bottles, 100 count (b)(4) cc bottles with (b)(4) CR caps (See NDA Section 3.2.P.7).

### B. Review, Comments and Recommendations

#### Drug Substance Hydrocodone bitartrate, USP

#### Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight



**Chemical Name(s):** Morphinan-6-one, 4,5-epoxy-3-methoxy-17-methyl-,(5 $\alpha$ )-, [R(R\*,R\*)]-2,3-dihydroxybutanedioate (1:1), hydrate (2:5)

4,5 $\alpha$ -Epoxy-3-methoxy-17-methyl-morphinan-6-one tartrate (1:1), hydrate (2:5)

Molecular formula:  $C_{22}H_{32}NO_{11} \cdot 1/2$

Molecular weight: 494.50

(b)(4)

The drug substance is manufactured by (b)(4) ( (b)(4) DMF (b)(4) or (b)(4) DMF (b)(4) Drug substance manufacturing sites are (b)(4) and (b)(4) and (b)(4) Complete addresses and contacts in the manufacturing facilities have been submitted to the NDA. LoAs to the drug substance DMFs are included in the NDA. The DMFs were most recently reviewed on 5/15/2012 and 6/1/2012 and deemed adequate. The applicant provided a comparative overview of the two APIs in Report ALK-001 (NDA Section 3.2.R). The two drug substances have different impurity profiles. The (b)(4) drug substance is manufactured from (b)(4) raw material and the (b)(4) from (b)(4). As a result, (b)(4) which is an (b)(4), but non genotoxic, is present in the (b)(4) but not in the (b)(4) API. The two API suppliers have a different specification for (b)(4) and this should be assessed during NDA review in

consultation with the Toxicology Division. In addition, note that the (b) (4) specification limit is expressed as % area in the (b) (4). The applicant should provide a Table of their own (Zogenix) drug substance acceptance specifications, as discussed during the pre-NDA meeting of November 18, 2011.

**Table 1. Comparisons of Specifications of API manufacturers**

Test	Specification Limits	
	(b) (4)	(b) (4)
Appearance	(b) (4)	
Solubility (Water)	(b) (4)	
Color Test (Optical Density/Water)	(b) (4)	
Identification A ( IR) (USP <197M)	(b) (4)	
Identification B (UV) (USP <197U>)	(b) (4)	
Specific Rotation (25°C)	(b) (4)	
pH (USP<791>)	(b) (4)	
Loss on Drying (105°C) (USP)	(b) (4)	
Residue on Ignition (USP<281>)	(b) (4)	
Chloride (Cl) (USP)	(b) (4)	
Ordinary Impurities (TLC) (USP<466>)	(b) (4)	
Organic Volatile Impurities (OVI)	(b) (4)	
Assay (HPLC) (USP)	(b) (4)	

Test	Specification Limits
Related Substances:     Unknown Related Substances Total Related Substances  (b) (4)	(b) (4)
Residual Solvents <sup>1)</sup>	
Particle Size US Standard No. 20 US Standard No. 45 US Standard No. 200	

(1) Supplier meets the USP <467> requirements for other organic volatile impurities (OVI)  
 NA = Not available from supplier's Certificates of Analysis. Please refer to each vendor's DMF for additional details.

In addition, the applicant stated that solid state properties of APIs, e.g., particle size distribution (PSD) are not impacting Critical Quality Attributes (CQAs) of the drug product, since the API is (b) (4) for processing. This claim should be assessed upon NDA review.

The reviewer should assess the USP listed HPLC methods, specified impurities, and criteria for all impurities carefully and compare them to what is being proposed by the applicant.

**Batch analyses**

Note that the applicant has not submitted to the NDA supporting CoAs for drug substance stability batches used for manufacture of primary stability batches of the drug product. These should be identified and be available for review, both for (b) (4) and (b) (4) batches, in the drug product DMF (b) (4)

**Drug product**

The drug product composition is reproduced below, in Table 2, from the Alkerme's DMF (b) (4) Amendment 8, submitted 4/27/2012. The drug product is based on the Alkerme's Spheroidal Oral Drug Absorption System (SODAS®) technology. The technology is based on coating sugar spheres with API and excipients to form the immediate release (IR) beads, and then coating the IR beads with rate-controlling polymer(s) to form the extended-release (ER) beads. No novel excipients are used in the formulation. The different strengths of capsules are achieved by (b) (4) keeping a fixed ratio IR:ER (20:80) beads.

**Table 2. Quantitative Composition for hydrocodone bitartrate extended-release capsules.**

Ingredient and Standard	Function	Composition (mg/capsule)					
		10	15	20	30	40	50
Hydrocodone Bitartrate, USP	Active	10.0	15.0	20.0	30.0	40.0	50.0
Sugar Spheres, NF (b) (4)	(b) (4)	(b) (4)					
Hypromellose (b) (4) USP (b) (4)							
Ammonio Methacrylate Copolymer Type (b) (4) NF (b) (4)	Controlled Release Polymer						
Silicon Dioxide, NF (b) (4)	(b) (4)						
Talc, USP							
<b>Total</b>							

**Pharmaceutical Development:**

The applicant included in the NDA *in vitro* abuse resistance studies and *in vitro* interactions with EtOH. Note that the rate-controlling polymer, (b) (4), is soluble in MeOH and EtOH, and the formulation is susceptible to alcohol dose dumping. *In vivo* alcohol interaction studies have been performed as well. Dissolution profiles of the 10 mg and 40 mg strengths in the presence of EtOH are reproduced below.

Figure 1a  
pH 6.8 Buffer with 0, 5, 20, and 40% (v/v) Ethanol (10 mg)

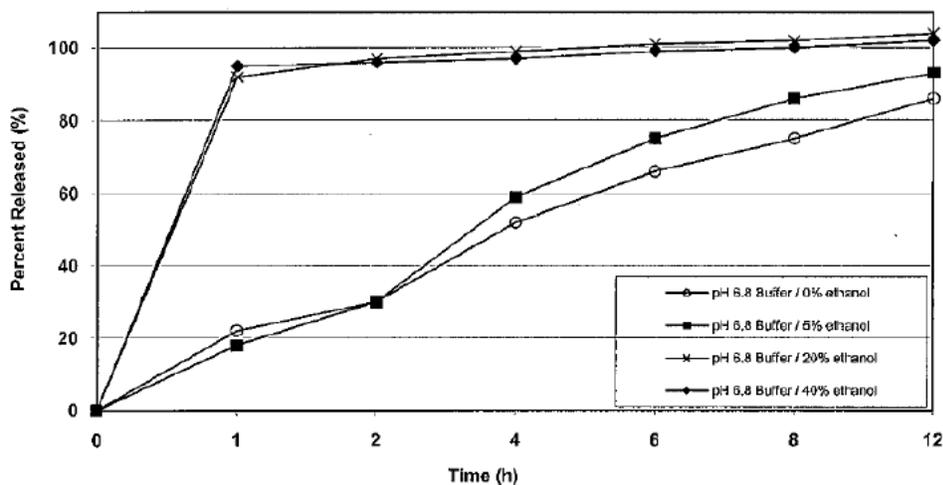
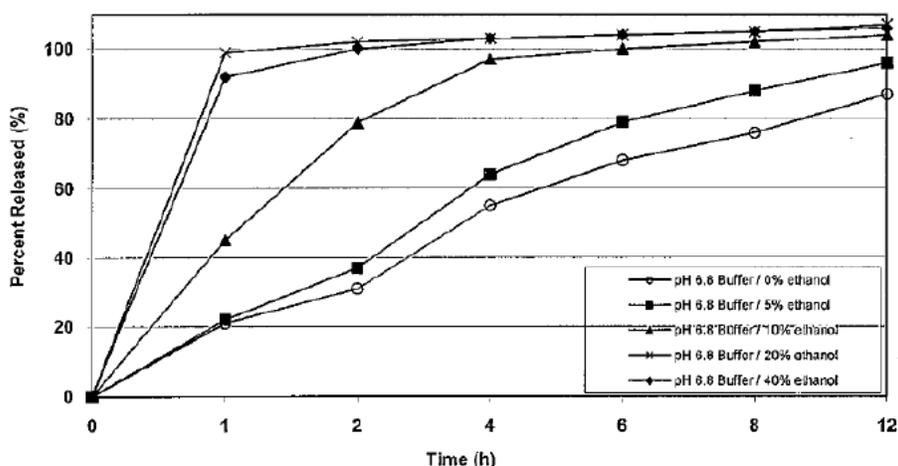


Figure 1b  
pH 6.8 Buffer with 0, 5, 10, 20, and 40% (v/v) Ethanol (40 mg)



Regarding abuse resistance, the following properties were evaluated: extraction (ground and unground powder), isolation, injectability in aqueous solution, nasal inhalation ( $D_{50}$  272  $\mu\text{m}$ ), rate of release and volatility. In general, disruption of the polymeric coating impacts the dissolution profile and releases the drug. Volatilization by direct heating was low (<35%) since the API is present in the salt form. Properties of the chosen excipients and their impact in the new formulation as well as (b) (4) manufacturing activities are included in DMF (b) (4). The Phase 1 clinical supplies have been manufactured in the Alkermes, Athlone, Ireland manufacturing site up to (b) (4) and the Phase 2, 3 clinical supplies in the Alkermes, Gainesville, GA site, which is the proposed manufacturing site, up to (b) (4) kg and (b) (4) kg, the proposed commercial scale. The manufacturing process and control strategies for drug product (b) (4) (IR and ER beads) are included in the drug product DMF (b) (4). Process validation for the commercial scale is planned post-approval. An IVIVC has been established during pharmaceutical development, which is included in DMF (b) (4).

### Manufacturing Process:

The proposed commercial manufacturer is Alkermes, Gainesville, GA with last FDA inspection in November 2011. Alkermes performs release and stability testing, as well as packaging. Alternate packaging facility is (b) (4) with last FDA inspection in March 2012. Batch formulae for drug product intermediates and final product strengths are included in the drug product DMF (b) (4). These should be reviewed and the production scale of final strengths should be confirmed based on combination of drug product intermediates. Hold times of drug product intermediates and bulk capsules should be available for review and supported by stability data. Proposed commercial batch scale is (b) (4) to (b) (4) capsules of the various strengths. Executed batch records are included in DMF (b) (4).

**Excipient control:** Analytical testing and specifications for excipients are included in the Drug Product DMF (b) (4). Hard gelatin capsules are sourced from (b) (4). Suppliers of the rest excipients are listed as well. Supporting CoAs for excipients used in the manufacture of clinical and primary stability batches should be identified and reviewed from executed batch records. The impact of excipient attributes in the manufacturability, quality and performance of the drug product should be assessed upon review of the drug product DMF (b) (4). Note that not all batch records of batches used in bioequivalence, bioavailability and primary stability batches are included in the drug product DMF, but the DMF holder stated that they are available at the site of manufacture.

**Drug Product Specifications:**

The proposed specifications are based on the specifications of API from (b) (4). Two degradants are controlled, (b) (4). The former exceeds ICHQ3B(R), based on a 3.0 g of total daily dose of hydrocodone bitartrate. None contains a structural alert. Impurities/degradants' specifications should be assessed as per ICHQ3B(R) in consultation with the Toxicology Division. The drug product specifications proposed in the NDA should be compared to drug product specifications in DMF (b) (4) and assessed for suitability for drug product manufactured both from (b) (4) and (b) (4) drug substances. The dissolution method and proposed dissolution specification, the method development, comparative dissolution profiles and the requested biowaiver (21CFR314.90) for the 15 mg strength, as well as the IVIVC should be assessed by the biopharmaceutics reviewer. Microbial controls have not been proposed for the drug product. With respect to microbial controls, the drug product is a low risk oral dosage form (hard gelatin capsules). However, the lack of microbial controls in the drug product specifications should be justified.

**Table 3. Proposed Specifications for Hydrocodone Bitartrate Extended-Release Capsules**

	TEST	Acceptance Criteria (Release and Stability)						Method Type
		10 mg	15 mg	20 mg	30 mg	40 mg	50 mg	
	Strength	(b) (4)						Method Type
	Material Code							
2.	Attribute Testing <sup>1</sup>	(b) (4)						Visual
3.	Identification A HPLC							(b) (4)
	Identification B <sup>1</sup> UV	(b) (4)						
4.	Assay							(b) (4)

	Related Substances (Any individual known impurity)	(b) (4)
	Related Substances (any individual unspecified drug-related degradation product)	
	Related Substances (Sum of all reportable impurities <math>< \frac{(b) (4)}{100}</math>)	
5.	Uniformity of Dosage Units by Content Uniformity <sup>1</sup>	
6.	Dissolution USP <711>	
	L1 % Release Each 6 of 6	
	L2, L3	
7.	(b) (4)	
8.	(b) (4)	

<sup>1</sup> For Release Testing Only

Acceptance criteria for appearance needs to be revised to indicate how the capsules appear with marking, letters, size of capsules, color, etc. Appearance should be monitored on stability.

**Batch analysis data:**

The 15 mg strength, batch RD021201 CoA has been included in the NDA as requested in the pre-NDA meeting. The scale is (b) (4) capsules. The batch analysis data indicate that the 15 mg batch met specifications with no detected impurities.

Additional CoAs for drug product lots and drug product intermediates are included in the drug product DMF (b) (4). However, not all primary stability lots and clinical lots are located in the batch analysis Section 3.2.P.5.4 of the DMF. Batch analysis data are hyperlinked to Appendices in Section 3.2.P.2. and 3.2.P.8.3 but not all batch details are clear (e.g., batch scale, batch analysis data). This should be assessed upon review at least for primary stability and clinical batches. If not clear, the DMF holder and the applicant should be asked to provide a clear table identifying batch numbers, scale, drug product intermediates and lots of API used for the ease of review.

Batch analysis data of representative lots met specifications with very low levels of impurities.

**Container Closure System:**

In Section 3.2.p.7 of the NDA, the applicant stated that they are currently seeking approval for the packaging configurations of (b) (4) (b) (4) and (b) (4) HDPE bottles and 100 ct (b) (4) (b) (4) HDPE bottles. There are several packaging configurations including (b) (4) in the drug

product DMF and proposed bridging to clinical packaging configurations. This should be assessed upon review of DMF (b)(4). Suitability of the container/closure system should be assessed.

**Stability:**

Stability testing of the drug product was performed at long-term (b)(4) RH), and accelerated (b)(4) RH) storage conditions. The applicant submitted Table 4, reproduced below, as a summary of the existing stability data. Details and identification of batches can be found in Section 3.2.P.8.1 of DMF (b)(4) and should be assessed. Up to 30 month normal storage data for bottle configurations are included in DMF (b)(4). The applicant requested a (b)(4) expiry for the (b)(4) ct bottles and 24 month expiry for the 100 ct bottles, based on existing data in primary and supporting stability batches. As discussed in the pre-NDA meeting, sufficient bridging of the packaging configurations to the clinical presentations will be assessed upon review of the NDA. The DMF holder performed photostability testing, testing of bulk capsules, and testing in open bottles, which should be assessed. The proposed expiration date(s) should be assessed.

**Labeling**

Labeling information on the container labels and packaging insert should be assessed with respect to CMC information. SPL labeling has not been included in M1 and should be requested.

**Table 4. Summary of Stability Batches**

Stability Study	Study Type <sup>1</sup>	Dosage Strength (mg)	Packaging Configuration	Storage Conditions	Study Duration	
					Planned (months)	Completed (months)
<b>HDPE Bottles – Registration Stability</b>						
STAB-018	Registration	10, 30, 40	(b)(4)	(b)(4)	36	36
					12	12
					6	6
STAB-018-2	Photostability	10, 20, 30, 40	NLT (b)(4) hours, NLT (b)(4)	(b)(4)	(b)(4)	(b)(4)
STAB-030	Clinical/ Registration	10 10 20, 30 40 50	(b)(4)	(b)(4)	(b)(4)	18 (on-going)
STAB-034	Registration	10, 50, 60,80	100 ct, (b)(4) bottle 100 ct, (b)(4) bottle	(b)(4)	(b)(4)	9 (on-going)
					(b)(4)	9 (on-going)
					6	6
		(b)(4)	Initial (on-going)			
		(b)(4)	0 (on-going)			
STAB-036	Registration (b)(4) API	10, 30, 50	100 ct, (b)(4) bottle	(b)(4)	(b)(4)	6 (on-going)
					(b)(4)	6 (on-going)
	Open Bottle	10, 50	100 ct, (b)(4) bottle		6	6
					1	1

Stability Study	Study Type <sup>1</sup>	Dosage Strength (mg)	Packaging Configuration	Storage Conditions	Study Duration	
					Planned (months)	Completed (months)
(b) (4)						
<b>In-Process Components</b>						
STAB-016	In-Process	IR Beads	(b) (4)	(b) (4)	12	12
STAB-017		SR Beads				
STAB-023		Bulk Capsules (10, 20, 30, 40)				
<b>HDPE Bottles – Supportive Stability</b>						
STAB-011	Clinical	10, 20, 30, 40	(b) (4)	(b) (4)	30	30
					6	6

<sup>1</sup> (b) (4), (b) (4) API used unless otherwise indicated

Note: Maximum duration for each given configuration is represented for each stability study, additional lots with less duration may also have been studied.

### 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. The two API suppliers have a different specification for (b) (4) and this should be assessed during NDA review in consultation with the Toxicology Division. In addition, the applicant should be asked to provide a Table of their own (Zogenix) drug substance acceptance specifications, which should include impurities controlled for both (b) (4) and (b) (4) APIs.
2. Supporting CoAs for drug substance lots used for manufacture of primary stability and clinical batches of the drug product should be identified in the drug product DMF (b) (4) and reviewed, both for (b) (4) and (b) (4) APIs.
3. Solid state properties of APIs, e.g., particle size distribution (PSD) have been claimed not to impact Critical Quality Attributes (CQAs) of the drug product, since the API is (b) (4) for processing. This claim should be assessed upon DMF (b) (4) review.
4. The manufacturing process and controls should be assessed in DMF (b) (4). Hold times of intermediates, e.g., IR beads, ER beads, bulk capsules and supporting stability data should be assessed.
5. Comparability of drug product manufactured from (b) (4) and (b) (4) APIs should be assessed.
6. Impurities/degradants' specifications should be assessed as per ICHQ3B(R) in consultation with the Toxicology Division. The drug product specifications proposed in the NDA should be compared to drug product specifications in DMF (b) (4) and assessed for suitability for drug product manufactured both from (b) (4) and (b) (4) drug substances. Suitability of the analytical methods, and its validation including LOD/LOQs should be assessed as per ICHQ2b(R).
7. The dissolution method and proposed dissolution specification, the method's development, comparative dissolution profiles, *in vitro* interaction with EtOH and the requested biowaiver (21CFR314.90) for the 15 mg strength, as well as the IVIVC should be assessed by the biopharmaceutics reviewer.
8. The lack of microbial controls in the drug product specifications should be justified.
9. "Abuse resistance" properties of the formulation, with respect to manufacturability, quality attributes, and performance of the drug product.
10. Identity of the primary stability batches, including API lots and drug product intermediates should be made clear during review. Batch scale based on scale of intermediates should be verified during review.
11. Proposed expiration dating is (b) (4) ( (b) (4) ct bottles) and 24 months (100 ct bottles). Bridging to clinical packaging configurations should be assessed.
12. Labeling in SPL format should be requested.

### D. Comments for the 74-day Letter:

None

- E. **Recommendation for fileability:** The NDA is fileable based on sufficient number of primary stability batches and real time stability data and pre-NDA agreements. The NDA is suitable for assessment based on FDA and ICH guidelines for submitting CMC information for New Drug Applications.

**Recommendation for Team Review:** The NDA is recommended for team review with a biopharmaceutics reviewer for evaluation of the biowaiver request, dissolution method/specification, comparative dissolution profiles and IVIVC.

**Biopharmaceutics, ONDQA assignment:** Reviewer: Akm Khairuzzaman  
The biopharmaceutics filing template is excerpted (Appendix A) from Dr. Khairuzzaman's filing review (6/17/12) in DARRTS, which recommends fileability from the biopharmaceutics perspective.

**Consults:**

- 1. Toxicology** (to be determined and initiated by the primary reviewer)

Danae D Christodoulou, Ph.D.  
CMC Lead, ONDQA

6/22/12  
Date

Prasad Peri, Ph.D.  
Branch VIII Chief, ONDQA

6/22/12  
Date

APPENDIX A: BIOPHARMACEUTICS				
	Parameter			Comment
1.	Is the QTTP (Quality Target Product Profile) defined for drug release? (3.2.P.2)	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	A list of QTTP has been provided which includes target PK profile. The drug products quality attributes included Dissolution.
2.	Has the risk assessment been performed to evaluate the criticality of the in vitro release? (3.2.P.2/3.2.P.5)	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	
3.	Is there any manufacturing parameter evaluated using in vitro release as an end point?	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	
4.	Is there any design space proposed using in vitro release as an end point?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>	
5.	Is the control strategy related to in vitro drug release? (3.2.P.2/3.2.P.5)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	
6.	Solubility (3.2.S.1)	High <input checked="" type="checkbox"/>	Low <input type="checkbox"/>	
7.	Permeability (2.7.1)	High <input type="checkbox"/>	Low <input type="checkbox"/>	Not Reported <input checked="" type="checkbox"/>
8.	BCS Class	I <input type="checkbox"/> II <input type="checkbox"/>	III <input type="checkbox"/> IV <input type="checkbox"/>	Unknown
9.	Is the study report included for the development of the in vitro release method? (3.2.P.2/3.2.P.5)	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	The dissolution method development report is provided in DMF- (b)(4)
10.	In the study report, are the individual data, the mean, the standard deviation and the plots provided?	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	
11.	Has the discriminating ability been shown for the in vitro release methodology using formulation variants? (3.2.P.2/3.2.P.5)	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	
12.	Is the justification provided for the acceptance criteria of the in vitro release? (3.2.P.2/3.2.P.5)	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	
13.	Are the proposed acceptance criteria adequate? (3.2.P.5)	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	Acceptance criteria appear to be reasonable. However, it requires further review in order to make a final decision
14.	Is the to-be-marketed formulation the same as that used in pivotal clinical trials?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>	The proposed commercial formulation (identified as Formulation 4 in application) was used for all of the clinical studies, following the initial phase I pharmacokinetic studies
15.	Are all the to-be-marked strengths used in the pivotal clinical trials?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>	For 15 mg strength there is a biowaver request in the application
16.	Have any biowaivers been requested? (1.12/2.7.1)	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	
17.	Is there any IVIVC information submitted? (5.3.1)	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	
18.	If the IVIVC information presented, are the study report and data provided?	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	

NDA Number: 202880

NDA Number and Type: 3S

Established/Proper Name:

Hydrocodone bitartrate extended-release capsules

Applicant: Zogenix

Letter Date: 05/01/2012

Stamp Date: 05/01/2012

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		IND 65,111, pre-NDA

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? <b>This question is not applicable for synthesized API.</b>			NA

7.	<p>Are the 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"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		<p>(b) (4) DMF (b) (4) (u) (4) DMF (b) (4)</p>
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"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	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"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?		X	This may have already been requested?
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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 (b) (4) and (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Referenced to DMF (b) (4) and (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Referenced to DMF (b) (4) and (b) (4)
15.	Does the section contain controls for the DS?	X		Specifications included in DMF (b) (4)
16.	Has stability data and analysis been provided for the drug substance?			Referenced to DMF (b) (4) and (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	

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		Referenced to DMF (b) (4)
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		Referenced to DMF (b) (4)
21.	Is there a batch production record and a proposed master batch record?		X	Referenced to DMF (b) (4) (Executed only)
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		Referenced to DMF (b) (4)
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		Referenced to DMF (b) (4)
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		Referenced to DMF (b) (4)

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	Solid 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		See below Packaging components in DMF (b) (4)

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	2	Alkermes	Oxycodone bitartrate extended-release capsules	3/23/2012	Drug product
(b) (4)	2	(b) (4)	Hydrocodone Bitartrate, (b) (4)	12/6/2011	API
(b) (4)	2	(b) (4)	Hydrocodone Bitartrate,	12/19/2011	API

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.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>			Based on sufficient body of data and pre-NDA agreements
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.	X		
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?		X	

*{See appended electronic signature page}*

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Name of

CMC Lead: Danae Christodoulou 6/22/12  
 Division III  
 Office of New Drug Quality Assessment

Date

*{See appended electronic signature page}*

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Name of

Branch Chief: Prasad Peri  
 Division III  
 Office of New Drug Quality Assessment

Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DANAE D CHRISTODOULOU  
06/22/2012  
Initial Quality Assessment

PRASAD PERI  
06/22/2012  
I concur