CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204307Orig1s000

CHEMISTRY REVIEW(S)

NDA 204-307

Hydrocodone Bitartrate and Chlorpheniramine Maleate Oral Solution

Cypress Pharmaceuticals, Inc.

Xiaobin Shen, Ph.D.
Division of Pulmonary, Allergy, and Rheumatology Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 204-307

2. REVIEW #: 1

3. REVIEW DATE: 2-Jan-2013

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	24-Apr-2012
Amendment 0002 & 0003	26-Jul-2012
Amendment 0007	31-Oct-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Cypress Pharmaceuticals, Inc.
Address:	135 Industrial Blvd., Madison, MS 39110
Representative:	Janet K. DeLeon, RAC
Telephone:	1-800-856-4393 ext. 120
Facsimile:	601-853-1567

Regulatory Agent Contact Information:

Chemistry Review Data Sheet

Address: 2944 W 143rd Ter,
Leawood, KS 66224

Representative: Janet K. DeLeon, RAC

Telephone: 913-681-0667

Facsimile: 913-681-0669

All communications regarding this NDA are requested to be sent to the regulatory agent.

8. DRUG PRODUCT NAME/CODE/TYPE:

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

- Chem. Type: 4
- Submission Priority: S

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

The application is filed on the basis of previously approved NDA and existing OTC monographs listed below:

Hydrocodone Bitartrate — Zutripro® Oral Solution, 5 mg/5 mL (hydrocodone bitartrate), NDA 022-439, Cypress Pharmaceuticals.
Chlorpheniramine Maleate — OTC monograph.

10. PHARMACOL. CATEGORY:

Hydrocodone bitartrate is antitussive (cough suppressing); Chlorpheniramine Maleate is antihistamine.

11. DOSAGE FORM: Oral Solution

12. STRENGTH/POTENCY: 5 mg Hydrocodone Bitartrate / 4 mg Chlorpheniramine Maleate per 5 mL.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__Rx ___OTC

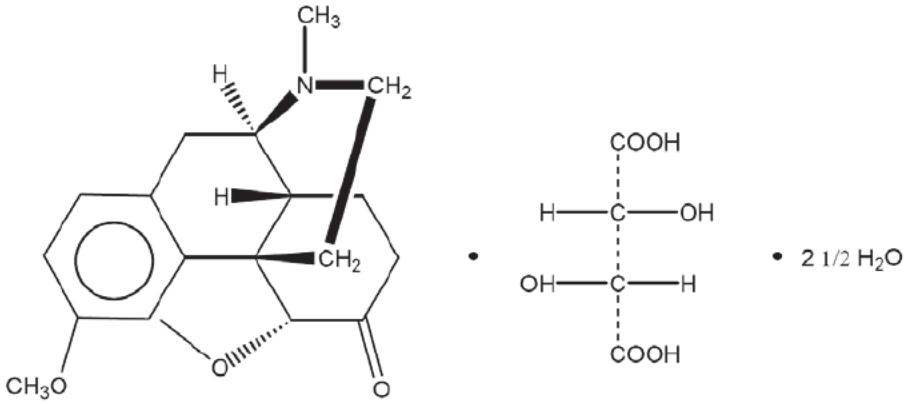
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

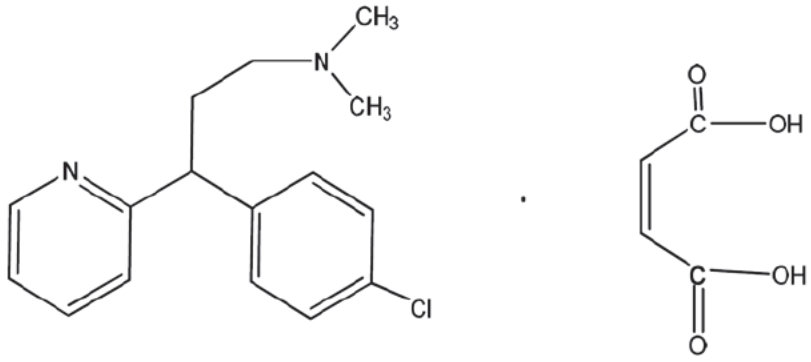
There are two active pharmaceutical ingredients in this product.

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



Molecular Formula: $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$
Molecular Weight: 494.490

Chlorpheniramine Maleate:
2-Pyridinepropanamine, γ-(4-chlorophenyl)-*N*,*N*-dimethyl-, (*Z*)-2-butenedioate (1:1)



Molecular Formula: $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$
Molecular Weight: 390.86

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	11-May-2012	NA
	II			3	Adequate	22-Feb-2012	NA
	IV			3	Adequate	26-Mar-2010	NA
	III			4	NA	NA	NA
	III			4	NA	NA	NA
	III			4	NA	NA	NA
	III			4	NA	NA	NA

[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:

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA	NA	NA
EES	Acceptable	2-Jan-2013	Dr. Derek Smith
Pharm/Tox	NA	NA	Dr. Carol Rivera-Lopez
Biopharm	NA	NA	NA
Methods Validation	Validation is not required by FDA Lab	27-Aug-2012	Dr. Xiaobin Shen
EA	Acceptable	27-Aug-2012	Dr. Xiaobin Shen
Microbiology	Pending	27-Aug-2012	Dr. Steven Donald

The Chemistry Review for NDA 204-307

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval.

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)

The drug product is a clear, colorless to light-yellow oral solution with a grape odor. It is indicated for relief of cough associated with common cold, and symptoms associated with upper respiratory allergies.

Each 5 mL of the solution contains 5.0 mg of hydrocodone bitartrate and 4 mg of chlorpheniramine maleate. In addition to the two active pharmaceutical ingredients, it contains excipients commonly used in oral solution products (e.g. water, citric acid, sodium citrate, sodium saccharin, sucrose, glycerin, propylene glycol, methylparaben, propylparaben and grape flavor). The commercial product is packaged in a 16 fl. oz. white HDPE bottle sealed with a white (b) (4) child resistant closure, (b) (4)

The process used to manufacture the commercial product (b) (4) is equivalent to that used for the product used in the clinical studies (b) (4)

There are two drug substances for this NDA: hydrocodone bitartrate and chlorpheniramine maleate.

1- Hydrocodone bitartrate (INN & USAN) syrup was approved by FDA and marketed as Hycodan® Syrup since 1988. Hydrocodone is a semi synthetic narcotic antitussive and analgesic. Hydrocodone is a white or slightly yellow-white powder that is soluble in water and slightly soluble in alcohol. It is manufactured by (b) (4) and referenced to DMF (b) (4) which was last reviewed in May, 2012 by Dr. Gil Jong Kang and found adequate. The status of the DMF's facilities is acceptable to CDER Compliance (per the EES). The applicant's release specifications for hydrocodone bitartrate comply with the USP monograph and include appearance,

identification, specific rotation, pH, loss on drying, residue on ignition, chloride, ordinary impurities, organic volatile impurities, assay, related substances (specified and unspecified), residual solvents, and microbial limits.

2- Chlorpheniramine maleate is an OTC monograph item. Chlorpheniramine is an antihistamine drug that prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa. Chlorpheniramine maleate is a white crystalline powder that is freely soluble in water and alcohol. It is manufactured by [redacted] (b) (4) and referenced to DMF [redacted] (b) (4) This DMF was last reviewed in Feb, 2012 by Dr. Gil Jong Kang and deemed adequate. The status of the DMF's facilities is acceptable to CDER Compliance (per the EES). The applicant's release specifications for chlorpheniramine maleate comply with the USP monograph and include appearance, identification, melting range, loss on drying, residue on ignition, assay, related substances (specified and unspecified), residual solvents, and microbial limits.

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

The drug product is an oral solution, each commercial package contains 16 fl. oz. [redacted] (b) (4) Each 5 mL of the oral solution contains 5 mg of hydrocodone bitartrate and 4 mg of chlorpheniramine maleate.

Dosing for adults is 5 mL every 4 to 6 hours as needed but not to exceed 4 doses (20 mL) in 24 hours. The manufacturer proposed a two year expiry with 20°C to 25°C storage condition, the firm provided 6 month real time stability data to support the two year expiry. The proposed expiry is granted based on the submitted stability data and the fact that this drug product formulation is practically the same as the Zutripro® oral solution approved with a 2 year expiry in NDA 22-439 except that this product does not have the pseudoephedrine hydrochloride component.

C. Basis for Approvability or Not-Approval Recommendation

From the perspective of chemistry, manufacturing and control, this drug product is recommended for approval.

The basis for approval include —

- The drug substances and product specifications provided adequate controls;
- The drug product excipients are of USP/NF grade;
- The drug product container closure systems are acceptable for use with oral solutions;
- Both drug substance and drug product are stable in the studied stability period and support the currently claimed 24 months of drug product expiry with support of the already approved NDA 22-439.

III. Administrative

A. Reviewer's Signature

Chemist: Xiaobin Shen, Ph.D.

B. Endorsement Block

ChemistName/Date: Xiaobin Shen
ChemistryTeamLeaderName/Date: Alan C. Schroeder
ProjectManagerName/Date: Youbang Liu

C. CC Block

65 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

XIAOBIN SHEN

01/02/2013

Recommend approval from CMC perspective.
There are comments at end of review to be communicated to the applicant.

PRASAD PERI

01/03/2013

I concur

Initial Quality Assessment (IQA) and Filing Review for Pre-Marketing Applications

Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 204307

2. SUBMISSION TYPE :Original
3. SUBMISSION NUMBER: 0

4. PRODUCT PROPERTIES: fixed two drug combination product (oral solution).

Trade or Proprietary Name:	Not yet proposed
Established or Non-Proprietary Name (USAN):	**Hydrocodone and Chlorpheniramine Oral Solution**
Dosage Form:	Oral Solution

5. NAME & ADDRESS OF APPLICANT:

Name:	**Cypress Pharmaceutical Inc.**
Address:	Post Office Box 399, Madison, MS 39130 (135 Industrial Blvd, Madison, MS 39110)
Representative:	Janet K. DeLeon, RAC Director of Product Development

6. SUBMISSION PROPERTIES:

Review Priority :	Standard
Classification (Chem. Code and Type):	Type 4S
Property (Legal Basis):	505(b)(2)

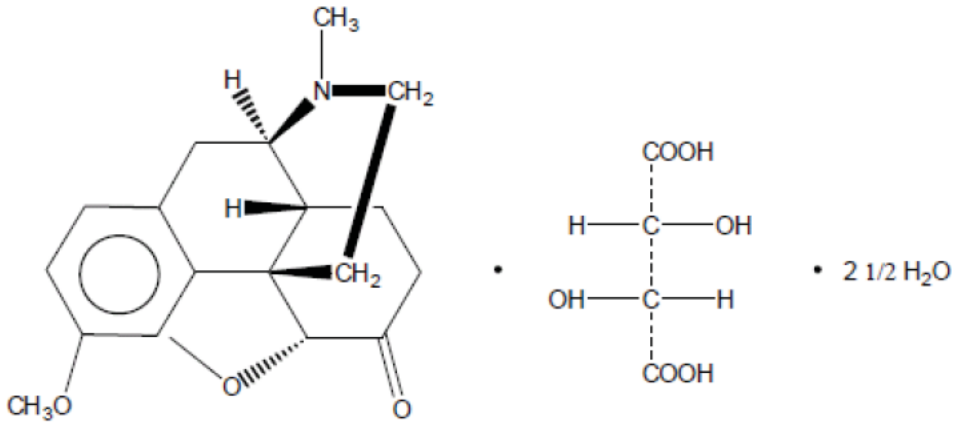
Responsible Organization:	DPARP

Review Information

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

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

2.3.S.1.2 Structure [Hydrocodone Bitartrate; (b) (4)

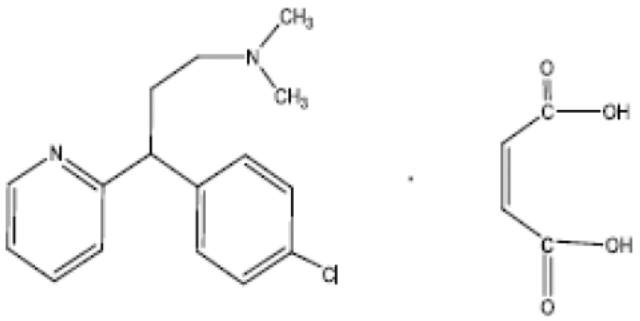


Molecular Formula: $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$

Molecular Weight: 494.490

2-Pyridinepropanamine, γ-(4-chlorophenyl)-N,N-dimethyl-, (Z)-2-butenedioate (1:1)

2.3.S.1.2 Structure [Chlorpheniramine Maleate; (b) (4)



Molecular Formula: $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$

Molecular Weight: 390.86

INDICATION: for relief of cough associated with the common cold and relief of symptoms associated with upper respiratory allergies.

2. PHARMACOLOGICAL CATEGORY: a semisynthetic centrally-acting opioid antitussive (hydrocodone bitartrate), and an antihistamine (chlorpheniramine maleate).

3. ROUTE OF ADMINISTRATION: oral

4. STRENGTH/POTENCY: hydrocodone bitartrate, USP, 5 mg and chlorpheniramine maleate, USP, 4 mg, per 5 mL.

5. Rx/OTC DISPENSED: X Rx ☐ OTC

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

Is this a SPOTS product? ☐ Yes X No ☐ Not evaluated at time of IQA.

7. RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II		(b) (4)	8/07/07	DMF (b) (4) was last reviewed on 3/29/12 and found adequate.
	II			12/02/11	DMF (b) (4) was last reviewed on 7/28/11 and was found to be adequate.
	III			1/31/12	
	III			2/13/12	
	IV				
	III			1/1/12	
	III			2/6/12	

b. Consults Recommended by CMC

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	☐	X	
Clin Pharm	☐	X	
EES	X		submitted 5/15/2012
Pharm/Tox	X	☐	possibly, e.g., for tox. testing of (b) (4) impurity in hydrocodone (see 3.2.P.5.5., pages 1-2).
Methods Validation	☐	X	

EA	☐	X	categorical exclusion request to be evaluated by the reviewer
New Drug Micro	X		yes, for antimicrobial effectiveness test and microbial limits
CDRH	☐	X	
Other	☐	X	

c. Other Applications or Submissions to note (if any):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
NDA 022439			Zutripro Oral Solution, Cypress Pharmaceutical, Inc.
NDA 22442			Rezira Oral Solution Cypress Pharmaceutical, Inc.
IND 102,177			hydrocodone, chlorpheniramine and pseudoephedrine oral solution Cypress Pharmaceutical, Inc.

d. Previous Communications with the Applicant to note (if any):

See item 4, filing review checklist section of this IQA.

Overall Conclusions and Recommendations

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	CMC Filing Issues
X	☐	1.

Are there potential CMC review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	CMC Comments for 74 Day Letter
X	☐	1. Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganisms of the Burkholderia cepacia complex. We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. Your test method should be validated and a discussion of those methods should be provided. Test methods validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested. 2. This pertains to the antimicrobial effectiveness and microbial limits tests which are referenced to USP (USP general chapters 51, 61 and 62). Provide a description of the actual procedures used as well as the results of method verification studies as appropriate. 3. There is an insufficient amount of stability (6 months) for the proposed 2 year expiry for the drug product. Provide sufficient stability data to support the proposed drug product expiry period, or shorten the expiry period appropriately.. 4. Provide a complete list of regulatory drug product specifications..

CMC Summary:
Critical Issues and Complexities

CMC Critical Issues or Complexities

It may be noted that the chlorpheniramine maleate impurities specification (drug substance) only controls total related compounds (max. [redacted] (b) (4) and [redacted] (b) (4) (max. [redacted] (b) (4) This should be checked against the specifications approved in the DMF, which has been adequate. In the batch analyses provided by the applicant, however, neither total related compounds nor [redacted] (b) (4) were detected (but the sensitivity of the method needs to be checked).

There are no stability data at the ICH Q1A(R2) intermediate storage conditions. This is at the applicant's risk.

The proposed expiry for the drug product is 2 years, however, stability data are only provided through 6 months for three batches of each drug product presentation. Six months of data normally does not warrant 2 years of expiry.

"No extractables or leachables from the container closure systems have been observed in the registration batches as shown in Section 3.2.P.8.3 by the lack of detection of any individual unknown impurities at 6 months, 40 °C/75% RH." This should be evaluated: it should be checked whether the analytical methods for degradation products in the drug product have adequate sensitivity, selectivity, etc. for expected leachables. Ideally, leachables should also be evaluated when the full shelf life of the product is reached.

The following information needs a pharm/tox evaluation: [redacted] (b) (4)

The stability results for degradation products, and for the parabens, are much lower in the data available (including accelerated data) so far, than the proposed acceptance criteria for these attributes, and the acceptance criteria could be tighter.

Drug product will only be stored in the horizontal position for post-approval stability studies. This is theoretically the worst case situation for drug product contact of container closure components.

The antimicrobial preservative effectiveness test will only be performed on stability, and will be performed only if the preservative assays fail to meet the specification. Per ICH Q1A, however, "a single primary stability batch of the drug product should be tested for antimicrobial preservative effectiveness (in addition to preservative content) at the proposed shelf life for verification purposes…" It is not clear whether this has been done.

The NDA proposes to fill two different container closure systems from three bulk batches of drug product. This is deemed to be sufficient to cover the requirement for three stability batches for each product presentation since the proposed product is an oral solution product.

See also additional comments following the drug product specifications below. See comments in the filing list.

Does the submission contain any of the following elements?

Nanotechnology	QbD Elements	PET	Other, please explain
☐	☐	☐	

Is a team review recommended?

Yes	No	Suggested expertise for team
☐	X	

Summary or Highlights of the Application ***(not already mentioned in other sections)***

Hydrocodone bitartrate drug substance CMC data are referenced to DMF [redacted] (b) (4) The hydrocodone bitartrate drug substance includes the USP monograph's acceptance criteria, plus tests and criteria for specified related substances, unknown related substances, total related substances, residual solvents, total aerobic microbial count and total combined yeasts and molds.

Chlorpheniramine Maleate drug substance CMC data are referenced to DMF [redacted] (b) (4) The chlorpheniramine maleate drug substance includes the USP monograph's acceptance criteria, plus tests and criteria for [redacted] (b) (4) residual solvents, total aerobic microbial count and total combined yeasts and molds.

The drug substance DMFs (see above) have previously been reviewed over the last year and were found to be adequate for these USP drug substances.

"This product is identical to a previously approved Cypress product, Zutripro® Oral

Solution (NDA 022439, approved on June 8, 2011), except for the absence of pseudoephedrine hydrochloride." This proposed drug product has not previously been marketed by this applicant, per a telephone inquiry from the Project Manager, Leila Hann.

Drug product composition:

Table 2.3.P-1. Unit Composition of Hydrocodone Bitartrate and Chlorpheniramine Maleate Oral Solution

Component	Reference to Quality Standards	Function	Unit Composition			
			% w/v	mg/mL	mg/5 mL	mg/480 mL
Hydrocodone Bitartrate	USP	Active ingredient	0.10	1.0	5.0	480
Chlorpheniramine Maleate	USP	Active ingredient	0.08	0.8	4.0	384
Citric Acid, Anhydrous	USP	(b) (4)				
Sodium Citrate (b) (4)	USP					
Sodium Saccharin	USP					
Methylparaben	NF					
Propylparaben	NF					
Sucrose	NF					
Glycerin (b) (4)	USP					
Propylene Glycol	USP					
Grape Flavor (b) (4)	In-house					
Water, Purified	USP					

NF = National Formulary.

Container closure configurations:

Table 2.3.P-2. Container Closure for Hydrocodone Bitartrate and Chlorpheniramine Maleate Oral Solution

Component	(b) (4)	Commercial Product (480 mL)
Container		16 fl oz, white HDPE bottle (b) (4)
Closure		(b) (4)
(b) (4)		

Drug product specifications:

Table 2.3.P-4. Specifications for Hydrocodone Bitartrate and Chlorpheniramine Maleate Oral Solution			
Test	**Acceptance Criterion**		**Analytical Procedure**
	Release	**Stability**	
Appearance/Description	Clear, colorless to light yellow liquid with a grape odor and free from precipitation	Clear, colorless to light yellow liquid with a grape odor and free from precipitation	Visual
Color	NMT (b) (4)	NMT (b) (4)	*SOP-QC-300*
Density[a,b]	(b) (4)		USP <841>
Viscosity[a]			USP <911>
pH[a]			USP <791>
Deliverable Volume[b,c]	Meets requirements	Not performed	USP <698>
Identification A:[b] Hydrocodone Bitartrate and Chlorpheniramine Maleate	Retention time of the APIs in the sample chromatogram match that of the standards	Not performed	*SOP-QC-287*
Identification B:[b] Hydrocodone Bitartrate and Chlorpheniramine Maleate	The UV absorption profiles of the major peaks in the chromatogram of the assay sample preparation is comparable to that of the standard preparation	Not performed	
Weight Loss	Not performed	Record	*SOP-QC-299*

Table 2.3.P-4. Specifications for Hydrocodone Bitartrate and Chlorpheniramine Maleate Oral Solution

Test	Acceptance Criterion		Analytical Procedure
	Release	Stability	
Assay:	(b) (4)		
Hydrocodone Bitartrate (5 mg/5 mL)			*SOP-QC-287*
Chlorpheniramine Maleate (4 mg/5 mL)			
Methylparaben (b) (4)			
Propylparaben (b) (4)			
Individual Unspecified Impurities			*SOP-QC-287*
Total Impurities			
Antimicrobial Effectiveness Test[d]			USP <51>
Total Combined Molds and Yeast Count			USP <61>
Total Aerobic Microbial Count			
Salmonella species			USP <62>
Escherichia coli			
Pseudomonas aeruginosa			
Staphlococcus aureus			
Packaging			Visual
(b) (4)			NA

[a] = Performed on bulk solution (for release).
[b] = Performed at release only.
[c] = (b) (4)
[d] = This test will be performed on the stability samples of commercial batches in the event that the preservative assays fail to meet the specification.
[f] = (b) (4)
LC = Label claim.
NA = Not applicable.

The drug product specifications include both release and stability specifications, yet there is only one set of regulatory specifications for the drug product. The stability specifications omit certain attributes (e.g., density, identification, deliverable volume, residual solvents), which is reasonable. Acceptance criteria for pH, assay, and paraben assay are broader for the stability specifications, which are the regulatory specifications. The antimicrobial effectiveness test will only be performed on stability, and only if the preservative assays fail to meet the acceptance criteria. See concerns about this expressed earlier in this review. Residual solvents are not tested on stability. Weight loss is only tested on accelerated stability for the registration batches: it needs to be evaluated whether this test should be also included in the post-marketing stability protocol(s)

"Three registration batches were manufactured by GSL at their facility in Houston, TX. A portion of each batch of bulk solution from Batches 28611, 28711 and 28911 was filled into two different packaging configurations (commercial and [redacted] (b) (4)." This approach is acceptable per discussion with Dr. Prasad Peri, Branch Chief, since the drug product formulation is a solution.
Description of Facility Related Risks or Complexities (i.e. number of foreign sites, large number of sites involved, etc.) – no apparent risks in this preliminary assessment.
See EES for complete list of facilities related to this application.

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	☐	Based on a cross section of pages in the CMC section.

4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X	☐	See our communications dated 6/11/2008 and 3/07/2012. We asked for justification of omission of leachables testing. In the NDA, it is indicated that no extractables or leachables were found from the container closure system, in the registration stability batches (see 3.2.P.2.4). This needs to be assessed for the sensitivity and capability of the methods. We requested validation data for method SOP-QC-287 which is provided in the NDA in Section 3.2.P.5.3. We asked that impurities and degradation products structurally similar to hydrocodone be monitored and qualified as necessary (pharm/tox comment probably). The drug substance specifications include three hydrocodone related specified impurities. See the discussion of characterization of impurities in section 3.2.P.5.5.

B. FACILITIES*				
	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.**	☐	☐	N.A. (drug substance is semisynthetic)

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	☐	All information except for e-mail address for hydrocodone d.s.; for chlorpheniramine maleate d.s., only name and phone number of US Agent (b) (4)
8.	Are drug product manufacturing sites are 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	☐	

9.	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: • 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	☐	

* 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	☐	Module 1, section 1.12.12. The claim of categorical exclusion is based on 21 CFR 25.31(b).

D. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X	☐	*See table on cover page.* LOAs are provided for both drug substances and for the commercial bottle and cap, and the sample bottle and cap.

E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
13.	Does the section contain a description of the DS manufacturing process?	☐	X	This information should be in the supporting DMF for each d.s. DMF (b) (4) for chlorpheniramine maleate d.s. was last reviewed on 3/29/12 and found adequate. DMF (b) (4) for hydrocodone bitartrate was last reviewed on 7/28/11 and was found to be adequate.
14.	Does the section contain identification and controls of critical steps and intermediates of the DS(in process parameters?	☐	X	This information is referenced to the supporting DMFs (see above).
15.	Does the section contain information on impurities?	☐	X	This information should be in the supporting DMFs (see above). The NDA does contain structures of potential impurities (from the DMF) for chlorpheniramine maleate and for hydrocodone bitartrate.
16.	Does the section contain information regarding the characterization of the DS?	☐	X	The DMFs are referenced (see above).
17.	Does the section contain controls for the DS?	X	☐	Both DS are compendial. Release specifications are provided; non-compendial analytical methods are summarized and validation is referenced to the supporting DMFs. Some validation summaries are provided in the NDA.
18.	Has stability data and analysis been provided for the drug substance?	☐	X	No stability data are provided, DMFs are referenced. Batch analysis data are provided in the NDA.
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	☐	X	Apparently not in the NDA
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	☐	X	Apparently not in the NDA
21.	Does the section contain container and closure information?	X	☐	Basic information is provided and the DMFs are referenced for additional information.

F. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
22.	Does the section contain quality controls of excipients?	X	☐	All compendial excipients will be tested to USP/NF monograph standards by USP/NF analytical procedures. The non-compendial excipient, Grape Flavor (b) (4), is tested by USP/NF procedures and the NDA contains specifications.
23.	Does the section contain information on composition?	X	☐	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X	☐	
25.	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	☐	(b) (4)
26.	Is there a batch production record and a proposed master batch record?	X	☐	Executed batch records are in Section 3.2.R, master batch records are in Section 3.2.P.3.3.
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	☐	X	No investigational section is provided; the formulation development summary provided in section 3.2.P.2.2 is based on the approved Zutripro Oral Solution NDA; this product contains one more active ingredient (pseudoephedrine) than the proposed drug product. See below re: the *in vivo* bioequivalence requirement.
28.	Have any biowaivers been requested?	☐	X	In the cover letter, the applicant indicates that they are not requesting a biowaiver. There is only one formulation composition being proposed. They indicate that they have studied in vivo bioequivalence and drug-drug interaction in the related Zutripo NDA. The FDA has found this approach to be reasonable in our 3/07/12 communication. This is a 505(b)(2) NDA.

29.	Does the section contain description of to-be-marketed container/closure system and presentations?	X	☐	The commercial product will be packaged in a 16 fl. oz. HDPE bottle containing 480 mL of the drug product formulation, plus a white (b) (4) child-resistant cap (b) (4) (b) (4)
30.	Does the section contain controls of the final drug product?	X	☐	Note that specifications for the registration batches are provided separately from specifications for the commercial batches. The only differences between these two sets of specifications appear to be the recording of weight loss in stability studies (registration batches), and in testing limitations described in the footnotes of the tables. Analytical methods are provided for non-compendial procedures. Specifics of the antimicrobial effectiveness and microbial limits test should be requested since they are only referenced to USP general chapters.
31.	Has stability data and analysis been provided to support the requested expiration date?	☐	X	All normal registration stability samples are stored in a horizontal position; photostability and thermal cycling studies were performed with upright containers. There are no stability data at the ICH Q1A(R2) intermediate storage conditions. Proposed expiry is 2 years, however, stability data are only provided through 6 months for three batches of each drug product presentation. No statistical calculation of expiry based on the data appears to have been done, and there appear to be too few stability data points for this at present. The expiry supported by the stability data is a review issue.
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	☐	X	none observed
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	☐	X	none observed

G. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
34.	Is there a methods validation package?	X	☐	

H. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	☐	☐	N.A.

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
36.	Has the draft package insert been provided?	X	☐	
37.	Have the immediate container and carton labels been provided?	X	☐	
38.	Does section contain tradename and established name?	☐	X	The established name is "hydrocodone bitartrate and chlorpheniramine maleate oral solution," and a proprietary name has not yet been proposed. Note that the labeled strength is in terms of the salt forms of both actives. The established name matches the strength of each active.

REVIEW AND APPROVAL

This document will be signed in DARRTS by the following:

CMC Lead or CMC Reviewer
Branch Chief

{See appended electronic signature page}

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

/s/

ALAN C SCHROEDER
06/07/2012

PRASAD PERI
06/08/2012
I concur