

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207768Orig1s000

CHEMISTRY REVIEW(S)

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 207768/000	Sponsor:	TRIS PHARMA INC
 de:	570		2033 ROUTE 130 STE D
Priority:	3		MONMOUTH JUNCTION, NJ 08852
Stamp Date:	30-JUN-2014	Brand Name:	CODEINE POLISTIREX AND CHLORPHENIRAMINE
PDUFA Date:	30-APR-2015	Estab. Name:	
Action Goal:		Generic Name:	
District Goal:	31-OCT-2014	Product Number; Dosage Form; Ingredient; Strengths	001; SUSPENSION; CHLORPHENIRAMINE MALEATE; 4MG 001; SUSPENSION; CODEINE PHOSPHATE; 20MG

FDA Contacts:	C. ABRAHAM	Prod Qual Reviewer	3017960612
	Y. LIU	Product Quality PM	3017961926
	S. NABAVIAN	Regulatory Project Mgr	(HFD-570) 3017962777
	C. BERTHA	Team Leader	3017961646

Overall Recommendation:	ACCEPTABLE	on 08-SEP-2014	by R. MOORE	()	2404029988
	PENDING	on 30-JUL-2014	by EES_PROD		

Establishment:	CFN: (b) (4)	FEI: (b) (4)	
	(b) (4)		
	(b) (4)		
DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE RELEASE TESTER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	30-JUL-2014		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	CFN: (b) (4)	FEI: (b) (4)	
	(b) (4)		
	(b) (4)		
DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE RELEASE TESTER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	19-AUG-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application: NDA 207768/000
Date: 30-JUN-2014
Priority: 30-APR-2015

Action Goal:
District Goal: 31-OCT-2014

Applicant: TRIS PHARMA INC
2033 ROUTE 130 STE D
MONMOUTH JUNCTION, NJ 08852

Brand Name: CODEINE POLISTIREX AND
CHLORPHENIRAMINE
Estab. Name:
Generic Name:

Priority: 3
Org. Code: 570

Product Number; Dosage Form; Ingredient; Strengths
001; SUSPENSION; CHLORPHENIRAMINE MALEATE; 4MG
001; SUSPENSION; CODEINE PHOSPHATE; 20MG

Application Comment:

FDA Contacts:	C. ABRAHAM	Prod Qual Reviewer	3017960612
	Y. LIU	Product Quality PM	3017961926
	S. NABAVIAN	Regulatory Project Mgr (HFD-570)	3017962777
	C. BERTHA	Team Leader	3017961646

Overall Recommendation: ACCEPTABLE on 08-SEP-2014 by R. MOORE () 2404029988
PENDING on 30-JUL-2014 by EES_PROD

(b) (4) - Confidential

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

(b) (4)

DMF No: (b) **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: MANUFACTURER FOR THE DRUG SUBSTANCE CHLORPHENIRAMINE MALEATE. (on (b) (4))

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					

SUBMITTED TO OC	(b) (4)				(b) (4)
OC RECOMMENDATION	30-JUL-2014			ACCEPTABLE	SAFAAIJAZIR

1 of 4

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

(b) (4)

DMF No: (b) **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: MANUFACTURER OF THE DRUG SUBSTANCE CODEINE PHOSPHATE. (on (b) (4))

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					

SUBMITTED TO OC	(b) (4)				(b) (4)
SUBMITTED TO DO PROFILE STILL INITIAL	30-JUL-2014	10-Day Letter			SAFAAIJAZIR
DO RECOMMENDATION	15-AUG-2014			ACCEPTABLE	MOBERT
THE MOST RECENT INSPECTION 9-12 JUNE 2014 WAS AN ABBREVIATED GMP INSPECTION COVERING THE QUALITY, MATERIALS, AND PACKAGING/LABELING SYSTEMS. NOT 483 WAS ISSUED AND WAS CLASSIFIED NAI. THE 2013 INSPECTION COVERED THE QUALITY, PRODUCTION, AND LABORATORY CONTROLS SYSTEMS AND WAS ALSO NAI AS NO 83 WAS ISSUED. BASED ON FILE REVIEW, (b) (4) COMMENTS ACCEPTABLE.					
OC RECOMMENDATION	19-AUG-2014			ACCEPTABLE	MOORER

Nabavian, Sadaf

From: ees_admin@fda.gov
Sent: Monday, September 08, 2014 3:13 PM
To: Abraham, Ciby; Bertha, Craig M; Godwin, Francis; Salganik, Maria*; Spain, Nancy *; Nabavian, Sadaf; Kyada, Yogesh*; Liu, Youbang
Subject: Overall OC Recommendation NDA 207768/000 Decision: ACCEPTABLE, Decision Date: 09/08/2014, Re-evaluation Date: 09/06/2015

This is a system generated email message to notify you that the Overall Compliance Recommendation has been made for the above Application.

For general questions about how to use EES in your work, send an email to EESQUESTIONS (EESQUESTIONS@cderr.fda.gov). To contact the EES technical staff, send an email to CDER EES Help (EESHELP@fda.hhs.gov). Thank you.

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

/s/

MARY GRACE LUBAO
05/13/2015

Chemistry Review Data Sheet

1. NDA 207,768
2. REVIEW #1
3. REVIEW DATE: 3/24/2015
4. REVIEWER: Ciby J. Abraham, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents
N/A

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
NDA-207768

Document Date
06-30-2014

Chemistry Review Data Sheet

a. Drug Master Files listed on 356h form or in DMF 27314*:

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE
27314	2	Tris Pharma, Inc.	Codeine polistirex/chlorpheniramine polistirex ER oral suspension	24-JUN-2014
(b) (4)	2	(b) (4)	(b) (4)	13-JUN-2013
	2			15-MAR-2013
	4			16-MAY-2013
	4			23-OCT-2012
	4			09-FEB-2012
	4			17-FEB-2012
	3			23-JUN-2011
	3			14-FEB-2013
	3			13-MAY-2009
	3			18-SEP-2012
	3			08-JUN-2009
	3			08-JUN-2009

(b) (4)	3	(b) (4)	(b) (4)	04-MAR-2013
	3			08-JUN-2009
	3			30-APR-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Tris Pharma Inc.

Address: 2033 Route 130 Suite D Monmouth Junction, NJ
08852

Representative: W. Scott Groner, Director of Regulatory Affairs

Telephone: 732-940-0358

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: TUZISTRA XR
b) Non-Proprietary Name (USAN): Codeine Polistirex and Chlorpheniramine Polistirex ER Oral Suspension
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: N/A
 - Submission Priority:

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

10. PHARMACOL. CATEGORY:

11. DOSAGE FORM: Oral suspension

12. STRENGTH/POTENCY: 14.7 mg codeine/2.8 mg chlorpheniramine

13. ROUTE OF ADMINISTRATION: Oral

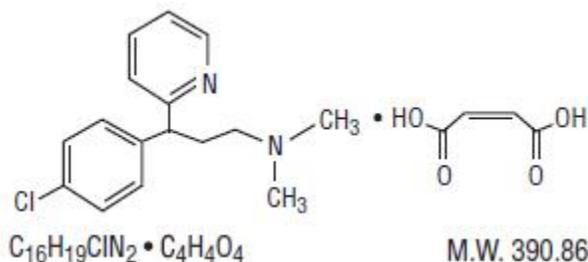
14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

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

Chlorpheniramine Maleate



Codeine Phosphate

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

See #6. All DMFs are up-to-date and adequate for this NDA.

B. Other Supporting Documents: N/A

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
NDA	21369	Codeprex	Listed drug product that is the basis for submission.

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	DATE	STATUS	REVIEWER/COMMENTS
EES	2/20/2015	Acceptable	Linda Ng
Biopharm	3/19/2015	Acceptable	Assadollah Noory
Microbiology	2/13/2015	Acceptable	Jessica Cole

Chemistry Review Data Sheet

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

Adequate information to support the manufacture, controls, and quality of the drug substances and drug product is provided in referenced DMFs for the Drug Substances and the Drug Product. Therefore, from the CMC standpoint, this application is recommended for approval.

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

N/A

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**

The first of two drug substances, chlorpheniramine maleate is manufactured by (b) (4) and is referenced in DMF# (b) (4). No additional information is given for this drug substance in this NDA. See Dr. Ciby J. Abraham's review for DMF# (b) (4) of 12/16/2014 for more details. The DMF is adequate for this NDA.

The second drug substance, codeine phosphate is manufactured by (b) (4) and is referenced in DMF# (b) (4). No additional information is given for this drug substance in this NDA. See Dr. Ciby J. Abraham's review for DMF# (b) (4) of 2/18/2015. The DMF is adequate for this NDA.

The drug product, Tuzistra XR is an extended-release oral suspension that contains codeine polistirex and chlorpheniramine polistirex. Tuzistra XR is manufactured by Tris Pharma, Inc. All of the required CMC data, including the manufacturing method, process controls, release specifications, batch analysis, and stability data is referenced to DMF 027314, which has been reviewed and found to be adequate. See Dr. Ciby J. Abraham's review for DMF# 027314 of 3/19/2015 for all pertinent CMC data.

Chemistry Review Data Sheet

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

The proposed indication for Tuzistra XR is for the relief of cough and (b) (4)
[REDACTED] upper respiratory allergies
in adults 18 years of age and older.

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided adequate information to support the manufacturing and controls of the drug substances and drug product. Based on the overall recommendation from the Office of Compliance, Microbiology and Biopharmaceutics, CMC therefore recommends the application for approval.

Executive Risk Assessment Summary

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**
Assay	Formulation Container closure Process parameters Scale/Equipment	L	-	-	-
Identification	Formulation Container closure Process parameters Scale/Equipment	L	-	-	-
Uniformity of suspension	Process parameter Equipment	L	-	-	The uniformity of suspension is low risk because the solution is shaken before use. The content uniformity results are within specification.
Microbial limits	Formulation Container closure Process parameters Scale/Equipment	L	-	-	-
Degradation Products	Formulation Container closure	L	-	-	-

Chemistry Review Data Sheet

	Process parameters Scale/Equipment				
Residual Solvents	Formulation Container closure Process parameters Scale/Equipment	L	-	-	-
Drug Release	Formulation Container closure Process parameters Scale/Equipment	M	-	-	See Assadollah Noory's review for details.

*Risk ranking applies to product attribute/CQA

**For example, post marketing commitment, knowledge management post approval, etc.

Drug Substance

Chlorpheniramine Maleate is manufactured by (b) (4) and is referenced in DMF# (b) (4). Please see Dr. Ciby J. Abraham's review for DMF# (b) (4) on 12/16/2014 for more details. The DMF is adequate for this NDA.

Codeine Phosphate is manufactured by (b) (4) and is referenced in DMF# (b) (4). See Dr. Ciby J. Abraham's review for DMF# (b) (4) of 2/18/2015. The NDA is adequate for this NDA.

Drug Product

The drug product, Tuzistra XR is an extended-release oral suspension that contains codeine polistirex and chlorpheniramine polistirex. Tuzistra XR is manufactured by Tris Pharma, Inc. The Sponsor references DMF 027314 for the manufacture, process controls, release specifications, batch analysis, and stability data. DMF 027314 has been reviewed and found to be adequate. See Dr. Ciby J. Abraham's review for DMF# 027314 of 3/19/2015 for additional details. A Certificate of Analysis for one batch of drug product is provided in the NDA and is shown below:

Chemistry Review Data Sheet

Description & Batch Analysis of Drug Product

Start of Sponsor Material.

Comparison between the Proposed Drug Product and currently Approved Drug Products:

	COD-CPM ER Oral Suspension	Penntuss®	Codeprex™ Pennkinetic®
Eq. Active Ingredient Strength (per 5 mL)			
Codeine Base	(b) (4)	10 mg	20 mg
Chlorpheniramine Maleate	4 mg	4 mg	4 mg
Eq. Active Ingredient in Single Adult Dose (10 mL)			
Codeine Base	(b) (4)	20 mg	40 mg
Chlorpheniramine Maleate	8 mg	8 mg	8 mg

Inactive ingredients are: purified water, sodium polystyrene sulfonate, ethyl maltol, povidone, triacetin, polyvinyl acetate, polysorbate 80, citric acid, sodium citrate, sucrose, starch, D&C Red No. 30, glycerin, methylparaben, propylparaben, propyl gallate, xanthan gum, cherry flavor.

Chemistry Review Data Sheet

Certificate of Analysis:

Codeine Polistirex and Chlorpheniramine Polistirex Extended Release Oral Suspension, eq. to 20 mg codeine phosphate and 4 mg chlorpheniramine maleate per 5 mL

Code: FP-101

Lot: TB-120A

Mfr Date: 04/20/13

Tests (Methods)	Specifications	Results
Description (M-101-ASY1)	Pink to reddish pink colored, viscous suspension.	Reddish pink colored viscous suspension
Identification		
A) HPLC Codeine (M-101-ASY1)	The retention time of the major peak in the chromatogram of the sample preparation corresponds to that in the chromatogram of the standard preparation as obtained in the assay	Conforms
B) UV-PDA Codeine (M-101-ASY1)	The UV spectrum of the major peak in the chromatogram of the sample preparation corresponds to that in the chromatogram of the standard preparation as obtained in the assay	Conforms
C) HPLC Chlorpheniramine (M-101-ASY2)	The retention time of the major peak in the chromatogram of the sample preparation corresponds to that in the chromatogram of the standard preparation as obtained in the assay	Conforms
D) UV-PDA Chlorpheniramine (M-101-ASY2)	The UV spectrum of the Chlorpheniramine peak in the chromatogram of the sample preparation corresponds to that in the chromatogram of the standard preparation as obtained in the assay	Conforms
pH (USP <791>)	Between 3.5 and 5.5	4.5
Deliverable Volume (USP <698>)	Average volume of 10 containers is not less than 100% of labeled volume, And no container is less than 95% of labeled volume (Applicable to products labeled to contain no more than 250 mL).	N/A
(b) (4) (M-101-ASY2)	Methylparaben: (b) (4) mg/mL (b) (4) %	(b) (4) mg/mL (b) (4) %
	Propylparaben: (b) (4) mg/mL (b) (4) %	(b) (4) mg/mL (b) (4) %
Assay (M-101-ASY1)	(b) (4) % of the labeled amount of Codeine phosphate, (b) (4)	A1: (b) (4) % A2: (b) (4) % Average: (b) (4) %
Assay (M-101-ASY2)	(b) (4) % of the labeled amount of Chlorpheniramine maleate	A1: (b) (4) % A2: (b) (4) % Average: (b) (4) %

Chemistry Review Data Sheet

Code: FP-101

Lot: TB-120A

Mfr Date: 04/20/13

Tests (Methods)	Specifications	Results	
Dissolution – Codeine phosphate, (b) (4) (M-101-DIS)		Averages (Range) L2 (b) (4)	
Dissolution – Chlorpheniramine maleate (M-101-DIS)		Averages (Range) L2 (b) (4)	
Microbial Limits (USP <61/62>)	Total aerobic microbial count does not exceed 100 cfu per g.	(b) (4) cfu/g	
	Total combined molds and yeasts do not exceed 10 cfu per g.	(b) (4) cfu/g	
	Absence of <i>Escherichia coli</i>	(b) (4)	
Impurity – Codeine phosphate, (b) (4) (M-101-ASY1)	Specified Impurities		
	Degradants		
	(b) (4)	NMT (b) (%)	(b) (%)
	(b) (4)	NMT (b) (%)	(b) (%)
	(b) (4)	NMT (b) (%)	(b) (%)
	(b) (4) ^b	NMT (b) (%)	(b) (%)
	(b) (4) ^b	NMT (b) (%)	(b) (%)
Unspecified Impurity	NMT (b) (%)	(b) (4) (%)	
Total Impurities	NMT (b) (%)	(b) (4) (%)	
Impurity – Chlorpheniramine maleate (M-101-IMP)	Unspecified Impurity:	NMT (b) (%)	
	Total Impurities:	NMT (b) (%)	
(b) (4)			

End of Sponsor Material.

Evaluation: Adequate. The sponsor provides details in DMF 27314.

Chemistry Review Data Sheet

Storage Statement: The drug product suspension will be placed in a 16 oz. amber ^(b) modern round container ⁽⁴⁾ with a proposed expiry of 24 months at 20°C to 25°C with excursions permitted to 15°C to 30°C.

A APPENDICES

A.1 Facilities and Equipment (biotech only) –N/A

A.2 Adventitious Agents Safety Evaluation –N/A

A.3 Novel Excipients –N/A

R REGIONAL INFORMATION

R1 Executed Batch Records – DMF 027314

R2 Comparability Protocols –N/A

R3 Methods Validation Package – N/A

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

Chemistry Review Data Sheet

**Evaluation:**

(b) (4)

(b) (4)

The Sponsor references Codeprex NDA 021369, which labels their product codeine polistirex and chlorpheniramine polistirex, both which are USAN names. CMC, labeling committee for OPQ, and the medical team came to an agreement that the Sponsor should use the USAN name and use the strength of the base for both drug substances which would be consistent with USP <1121> Monograph "Naming Policy for Salt Drug Substances in Drug Products." Therefore, the medical team will send out an IR stating that the label should be: "*Tuzistra® XR (codeine polistirex and chlorpheniramine polistirex) extended-release oral suspension*" with the strengths expressed as "14.7 mg codeine and 2.8 mg chlorpheniramine." Further a statement of equivalence to the respective codeine phosphate and chlorpheniramine maleate salts is included in the package insert. An updated carton label has not been provided. Once the sponsor responds to the labeling IR, they are instructed to provide an updated carton package as well.

B. Environmental Assessment Or Claim Of Categorical Exclusion

Chemistry Review Data Sheet

Start of Sponsor Material.

Tris Pharma Inc. (Tris) claims an exclusion to the preparation and submission of an Environmental Assessment under 21 CFR 25.31(a). This section specifies that for human drugs and biologics, preparation of an Environmental Assessment or Environmental Impact Statement is not required under a categorical exclusion for, as in this case, action on an NDA, if the action does not increase the use of the active moiety. This is a 505(b)(2) application for a novel codeine/chlorpheniramine formulation. The reference listed drug is Codeprex™ Pennkinetic® (UCB Inc., NDA 021369), which has been approved since 2004. Furthermore, codeine and chlorpheniramine are OTC monograph drug listed in 21 CFR 341 as antitussive and an antihistamine agent, respectively. The introduction of Tris' product would be another form of the already marketed active ingredients, codeine and chlorpheniramine, and so their use would not increase the overall use of the active moiety. Tris also states that, no extraordinary circumstances, as defined under 21 CFR 25.21, exist which would preclude the categorical exclusion.

End of Sponsor Material.

Evaluation: Adequate. The sponsor claims categorical exclusion under 21 CFR 25.31(b).

III. List of Deficiencies Sent to Sponsor – None, the sponsor referenced DMFs for the drug substances and drug product.

Chemistry Review Data Sheet

Ciby J. Abraham, Ph.D.
Acting Quality Assessment Lead
OPQ/ONDP/DIVII/Branch IV

Julia C. Pinto, Ph.D.
Acting Branch Chief
OPQ/ONDP/DIVII/Branch IV

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

/s/

CIBY J ABRAHAM
03/24/2015

JULIA C PINTO
03/25/2015

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre- Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

I. Review Cover Sheet

1. OMPQ Reviewer: Linda Ng, Ph.D.
2. NDA Number: NDA 207768
Submission Date: June 30, 2014
21st C. Review Goal Date: February 30, 2015
PDUFA Goal Date: April 30, 2015

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Tuzistra XR
Established or Non-Proprietary Name (USAN) and strength:	Codeine Polistirex and Chlorpheniramine Polistirex ER Oral Suspension, 20 mg/4 mg per 5 mL
Dosage Form:	Oral Suspension

4. SUBMISSION PROPERTIES:

Review Priority :	STANDARD
Applicant Name:	Tris Pharma Inc
Responsible Organization (OND Division):	DPARP

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

II. Application Detail

1. INDICATION: Relief of cough and (b) (4)
other upper respiratory allergies.
2. ROUTE OF ADMINISTRATION: Oral
3. STRENGTH/POTENCY: 20 mg codeine and 4 mg chlorpheniramine in 5 mL
4. Rx/OTC DISPENSED: Rx OTC
5. ELECTRONIC SUBMISSION (yes/no)? yes
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V		X		
2.	Breakthrough Therapy Designation		X		
3.	Orphan Drug Designation		X		
4.	Unapproved New Drug		X		
5.	Medically Necessary Determination		X		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		X		
7.	Rolling Submission		X		
8.	Drug/device combination product with consult		X		
9.	Complex manufacturing		X		
10.	Other (e.g., expedited for an unlisted reason)		X		

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

III. FILING CHECKLIST

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

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	Yes	No	Comment
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		The 356h is not complete. The drug substance facilities are missing. The firm has been asked to update.
12.	Do all sites indicate they are ready to be inspected (on 356h)?	X		
13.	Is a single comprehensive list of all involved facilities available in one location in the application?		X	See item #11
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	X		All testing performed in the respective ds or dp manufacturing facilities.
15.	Additional notes (non-filing issue)	X		
	1. Are all sites registered or have FEI #?			
	2. Do comments in EES indicate a request to participate on inspection(s)?		X	
	3. Is this first application by the applicant?		X	

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
16.	Have any Comparability Protocols been requested?		X	

IMA CONCLUSION				
	Parameter	Yes	No	Comment
17.	Does this application fit one of the EES Product Specific Categories?		X	
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	X		356h does not include the ds manufacturers. All sites have been updated with final recommendation.
19.	From a CGMP/facilities perspective, is the application fileable? If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements? No			
Nanotechnology <input type="checkbox"/>	RTRT Proposal <input type="checkbox"/>	PAT <input type="checkbox"/>	Drug/Device Combo <input type="checkbox"/>
PET <input type="checkbox"/>	Design Space <input type="checkbox"/>	Continuous Mfg <input type="checkbox"/>	Naturally derived API <input type="checkbox"/>
Other (explain):			

Manufacturing Highlights

1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	Codeine phosphate DMF (b) (4) Chlorpheniramine Maleate DMF (b) (4)

Include process flow chart/diagram (see eCTD Section 2.3.S.1)

2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	Manufacturing process described in DMF 27314

Include process flow chart/diagram (see eCTD Section 2.3.P.1)



(b) (4)

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
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3. **Drug Product Facility Inspectional History that could impact the manufacturing of this product** None. All facilities have been inspected recently.

Additional information not covered above

None

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
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Manufacturing Facilities Chart (generated from 602A DARRTS report and OMPQ macro):

For each EER, indicate PAI recommendation on the Manufacturing Facilities Chart above (e.g., PS, GMP, 10 Day, AC based on file review). This is the recommendation that will be entered into EES. **For PAI, include the reason for the PAI (i.e. PAI Trigger) in the comment section of the facilities chart.**

NDA:		207768 Codeine Polistirex and Chlorpheniramine Polistirex ER Oral Suspension								
		(eq. 20 mg Codeine Phosphate and 4 mg Chlorpheniramin)								
Sponsor:		TRIS PHARMA INC								
Indication:		Relief of cough and (b) (4) upper respiratory allergies.								
PDUFA:		9/9/2015 under STANDARD Review								
Responsible Organiz:		CDER/ODEII/DPARP								
EERS Submitted By:										
Chart Generated On:		9/15/2014								
		Overall OC Recommendation: ACCEPTABLE entered into EES on 9/8/2014 3:05:12 PM								
		Reevaluation date: 9/6/2015								
Establishment Name	EER Creation Date	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Firm Profiles - Current Status	Inspection History, Dates, Classifications	Most Recent Milestone	Most Recent EER Compliance Status
				(b) (4)	Drug substance manufacturer and release tes ing	CSN	(b) (4)	(b) (4)	OC RECOMMENDATION	AC
					Drug substance manufacturer and release tes ing	CSN	(b) (4)	(b) (4)	OC RECOMMENDATION	AC
TRIS PHARMA INC	7/30/2014	3004712471	NWJ	USA	Drug product manufacturer, packager, release and stability testing	SES	http://intranetapps.fda.gov/scripts/mpqa/profile.cfm?FEI=3004712471	Acceptable from 1/14/2014 inspection	OC RECOMMENDATION	AC

V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no, Yes to questions 11-12) Yes
Based on Section IV, is a KTM warranted for any PAI? (yes/no). If yes, please identify the sites in the above chart. No; all facilities have been inspected recently and will not be inspected for this NDA
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no)
Comments for 74 Day Letter
1.
2.
3.

REVIEW AND APPROVAL (DARRTS)

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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.

/s/

LINDA L NG
09/26/2014

MAHESH R RAMANADHAM
10/02/2014

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

APPLICATION INFORMATION

1. NEW DRUG APPLICATION NUMBER: N207768 with reference to DMF 27314.¹

Tuzistra (codeine polistirex and chlorpheniramine polistirex ed-

(b) (4)

er

IND

(b) (4)

(b) (4)

(b) (4)

the applicant

given in terms of the codeine and

chlorpheniramine free bases. The drugs are initially codeine phosphate and chlorpheniramine maleate, from (b) (4) (DMF (b) (4)) and (b) (4). (DMF (b) (4)) prior to their conversion by Tris Pharma (b) (4). The codeine phosphate with product code (b) (4), under DMF (b) (4) was recently found to be acceptable to be used in an oral solution drug product (see review dated 06-JUN-2012). The chlorpheniramine maleate from (b) (4), under DMF (b) (4), was recently found to be acceptable to be used in an oral solution drug product (see review dated 21-MAR-2014).

¹ The NDA 207768 and the referenced DMF 27314 are both from Tris Pharma Inc., so this review will include information and data from both of these sources. Note that the bulk of the drug product information for this NDA is included in the DMF 27314. Although this initial filing review/IQA includes data and information from both the NDA and the DMF, IR comments compiled during the CMC review will need to be sent to the respective owner or holder, depending on the location of the sources of the data and information in question.

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Same or New Indication). Previously there were two different codeine polistirex/chlorpheniramine polystirex extended release oral suspensions approved but both have been discontinued from the market (Penntuss® NDA 18928 and Codeprex® NDA 21369).

3. RECEIVED DATE: 30-JUN-2014 (Applicant: Tris Pharma Inc.)

4. RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form or in DMF 27314*:

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
27314	2	Tris Pharma, Inc.	Codeine polistirex/chlorpheniramine polistirex ER oral suspension	24-JUN-2014	This file has not been reviewed as of yet
(b) (4)	2	(b) (4)	(b) (4)	13-JUN-2013	Last review 21-MAR-2014; no subsequent amendments/ARs
	2			15-MAR-2013	Last review 06-JUN-2012; subsequent amendments/ARs not reviewed
	4			16-MAY-2013	Last review 14-APR-2014; subsequent amendments/ARs not reviewed
	4			23-OCT-2012	No recent review
	4			09-FEB-2012	Last review 04-APR-2012; subsequent amendments/ARs not reviewed
	4			17-FEB-2012	Last review 19-NOV-2009; subsequent ARs not reviewed
	3			23-JUN-2011	No recent review
	3			14-FEB-2013	Last review 26-AUG-2011; subsequent amendments/ARs not reviewed
	3			13-MAY-2009	Last review 24-JAN-2012; subsequent ARs not reviewed
	3			18-SEP-2012	Last review 31-JAN-2012; subsequent amendments/ARs not reviewed
	3			08-JUN-2009	Last review 10-FEB-2012; subsequent ARs not reviewed
	3			08-JUN-2009	Last review 12-MAR-2012; subsequent ARs not

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(b) (4)	3	(b) (4)	(b) (4)	04-MAR-2013	reviewed Last review 29-MAY-2014; Adequate
	3			08-JUN-2009	No recent review
	3			30-APR-2008	Last review 07-MAY-2009; subsequent amendments/ARs not reviewed

b. Recommended Consults

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	X	<input type="checkbox"/>	Request evaluation of stability data if trends in parameters appear to limit expiry and applicant's analysis is suspected of being deficient.
Clin Pharm	<input type="checkbox"/>	X	
EES	X	<input type="checkbox"/>	ONDQA PM submitted EER to the Office of Compliance on 30-JUL-2014 (current recommendation is PENDING)
Pharm/Tox	X	<input type="checkbox"/>	<p>After review of the DMF for the flavoring (b) (4), it may be necessary to request that the pharmacologist evaluate any flavoring components that are not sanctioned for use in food or drugs (as per 21 CFR 172.510 and 172.515, etc.).</p> <p>The reviewer may need to informally consult the pharmacologist as the DMF 27314 contains (b) (4) g toxicological information in DM (b) (4)</p> <p>The drug product specification includes a limit of NMT (b) (4) for the (b) (4) impurity. In the past, this is acceptable as long as data are provided to shown that this is a nongenotoxic impurity. The reviewer can informally consult with the pharmacologist regarding this particular structural alert containing impurity.</p> <p>Neither the application nor the DMF 27314 addresses the potential for drug product container closure leachables. The reviewer should review the application in line with the recommendations of section III.F. 1 of the Agency <i>Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics</i> (1999). A consult to the pharmacologist may be necessary if additional data are deemed necessary and are requested and received.</p>

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Methods Validation	<input type="checkbox"/>	X	Left to reviewer discretion if any drug product methods are questionable, but codeine and chlorpheniramine are not NMEs so it is not mandatory that any methods be assessed by the Agency laboratory.
EA	<input type="checkbox"/>	X	Applicant claims a categorical exclusion under 21 CFR 25.31(a), and states that action on the application will not increase the use of the active moiety.
New Drug Micro	<input type="checkbox"/>	X	The oral suspension drug product is not sterile and the specification is consistent with recommendations of USP <1111> for aqueous preparations for oral use. The microbiology team has been notified (18-JUL-2014) of the application and will determine if any microbiology review is needed.
CDRH	<input type="checkbox"/>	X	N/A
Other	<input type="checkbox"/>	X	N/A

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

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND	Submitted 30-JUL-2013, currently active	(b) (4)	Codeine polistirex and chlorpheniramine polistirex ER suspension

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d. Previous Communications with the Applicant to note (see module 1.6.3 for complete detail):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
Study May Proceed Letter	18-SEP-2013	IND (b) (4)	This letter included comments from the biopharmaceutics team
Information Request Letter	15-AUG-2013	IND (b) (4)	CMC comments related to the calculation of the strength of the drug product
Meeting Minutes	03-DEC-2012	IND (b) (4)	Discussion of stability data requirements for NDA at the 26-OCT-2012, meeting
Written Response	14-SEP-2012	IUND (b) (4)	Written response to the questions posed for the 26-OCT-2012, meeting

OVERALL PRODUCT QUALITY CONCLUSIONS AND RECOMMENDATIONS

Is the Product Quality Section of the application fileable from a CMC perspective?

Yes	No	CMC Filing Issues
X	<input type="checkbox"/>	N/A

Are there potential CMC review issues to be forward to the Applicant with the 74 day letter?

Yes	No	
<input type="checkbox"/>	X	

Is the Product Quality Section of the application fileable from a biopharmaceutics perspective?

Yes	No	Biopharmaceutics Filing Issues
X	<input type="checkbox"/>	

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Are there potential biopharmaceutics review issues to be forward to the Applicant with the 74 day letter?

Yes	No	Biopharmaceutics Comments for 74-Day Letter:
X	<input type="checkbox"/>	<ol style="list-style-type: none"> 1. Please provide detailed report of dissolution method validation. 2. Please provide detailed report of the IVIVC model development. 3. Justification for ER claim

Does the submission contain any of the following elements?

	Yes	No	Comments
Botanical Products	<input type="checkbox"/>	X	
Combination Products	<input type="checkbox"/>	X	
Nanotechnology	<input type="checkbox"/>	X	
PET	<input type="checkbox"/>	X	
QbD Elements	<input type="checkbox"/>	X	
SPOTS	<input type="checkbox"/>	X	

Is a team review recommended?

Yes	No	Suggested expertise for team
<input type="checkbox"/>	X	

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Drug Product Risk Assessment

DP attribute/ CQA	Factors that can impact the CQA	O ²	S ^{4,3}	D ⁴	FMECA RPN #	Comment & considerations
Assay	<ul style="list-style-type: none"> incorrect amount of APIs formulated high impurity levels in input APIs high level of degradation of APIs as formulated Inhomogeneity during filling of CCSs 	3	3	1	9	<ul style="list-style-type: none"> GMP adherence should prevent incorrect API amounts formulated; drug product formulation adjusted by assay of codeine polistirex (b) (4) (b) (4) Acidic formulation (pH range 3.5-5.5), (b) (4) amber bottle, (b) (4) (propyl gallate) (b) (4) (b) (4) Acidic pH assured by formulation buffer IPC for uniformity for both drugs applied to formulation suspension bulk (top, middle, bottom assay)
Identification	<ul style="list-style-type: none"> incorrect drugs formulated no drug formulated 	1	3	1	3	<ul style="list-style-type: none"> Probability of occurrence should be low and detectability high if applicant adheres to GMPs: specifications for both drug substances include specific identification testing (IR spectra) (b) (4) Severity of failure would depend on situation (incorrect or no drug present); not possible to predict Final drug product specification includes two non-specific tests for each drug for identity confirmation
Uniformity of	<ul style="list-style-type: none"> Inhomogeneity during 	2	3	4	24	<ul style="list-style-type: none"> IPC for uniformity for both drugs applied to formulation

² O = Probability of Occurrence; S = Severity of Effect; D = Detectability

³ Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs.

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Drug Product Risk Assessment

suspension	filling of CCSs <ul style="list-style-type: none"> Settling of suspension-based formulation during shelf life 				suspension bulk (top, middle, bottom assay) <ul style="list-style-type: none"> Formulation contains (b) (4) and xanthan gum (b) (4); adherence to GMPs will assure correct content of these components Drug product labeling will instruct patients to “shake well before using” Unclear that current Description test method examines for formulation settling (applied at release and for stability testing) Unclear if current assay methods include product shaking prior to sample preparation Freeze-thaw studies (12 days w/3 cycles) showed formulation remained uniform
Microbial limits ⁴					<ul style="list-style-type: none"> Final drug product microbial limits requirements in specification consistent with USP <1111> Methyl- and propyl-parabens (b) (4) Microbial limits testing is performed on the non-compendial (b) (4) and some of the compendial excipients (water, sucrose, D&C Red #30 (b) (4), xanthan gum) Microbial limits acceptance criteria met for product in stability studies
Degradation Products	<ul style="list-style-type: none"> high impurity levels in input APIs high level of degradation of APIs as formulated 	2	3	1	6 <ul style="list-style-type: none"> Acidic formulation (pH range 3.5-5.5), (b) (4) amber bottle, and (b) (4) (b) (4) (b) (4)

⁴ Evaluation to be done by the microbiology team (as per microbiology pilot).

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Drug Product Risk Assessment

							(b) (4)
Residual Solvents ⁵	<ul style="list-style-type: none"> Incomplete (b) (4) 	1	3	1	3		<ul style="list-style-type: none"> Formulation also contains propyl gallate (b) (4) Acidic pH assured by formulation buffer
Drug Release	<ul style="list-style-type: none"> Insufficient (b) (4) 	2	3	5	30		<ul style="list-style-type: none"> Other than assay and purity, there are no CQAs of the drug substance that would impact the CQA of drug release of the drug product, (b) (4) Drug release (dissolution) is tested for both actives at release and for routine stability batches IPC for dissolution is applied to (b) (4) chlorpheniramine polistirex (used in formulation) IPC for dissolution (1 and 3 hours) is applied to the final (b) (4) codeine polistirex that is used in the formulation 40% alcohol exposure increases the codeine release so that f2 criteria is not met for the dissolution profile Labeling warns against taking drug product with alcohol

⁵ Applicant refers to Residual Solvents as a CQA drug product, but it is more appropriate to classify it as a CQA for the drug substance.

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CMC Summary: Critical Issues and Complexities

(This section is formatted to expand as far as needed by author.)

- Tris Pharma had submitted IND (b) (4) for the support of the development of the drug product of this NDA. We had no formal meetings with Tris Pharma, although we did provide them with responses to their questions for a pre-IND meeting request (subsequently the meeting was cancelled). As already mentioned, the sponsor was informed that they should include at least 12 months of real-time stability data and 6 months of accelerated stability data with the application. The size of these three “test” or primary stability batches is (b) (4) smaller than the intended production batch size. Note that the applicant is proposing a 24 month expiry period. The applicant has not performed a statistical analyses of the stability data, but has provided plots showing some trending parameters (only assay and impurities data plotted) in P.8.1.
- The labeling indicates that patients are to shake the drug product prior to use. It is unclear from the stability data whether or not any settling or caking of the formulation occurs with time. Nor is it clear whether or not assay or content uniformity samples are obtained from shaken or unshaken drug product. More information will be needed to clarify these issues.
- Most of the excipients used in the drug product are of compendial grade, however, the formulation also includes (b) (4) starch and a cherry flavoring that are not of compendial grade. Information about these non-compendial excipients should be evaluated and the pharmacology/toxicology team consulted if necessary, depending on the components comprising these excipients. All of the compendial excipients were used in other oral suspension drug products, with the exception of propyl gallate, which was used in other solid oral dosage forms, but not an oral suspension. It is not known how the concentrations translate and compare in terms of daily intake, or if the associated diseases might warrant different risk-benefit ratios to come into play with regard to the excipient daily intake. The pharmacology/toxicology team may need further information regarding the concentrations of the various excipient components regarding any necessary assessment or determination of qualification.
- The issue regarding the presentation of the established name and strength of the product in terms of the free bases will need to be addressed by the applicant. This was brought to the applicant’s attention first during the initial

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IND safety review but remains unresolved.

- The formulation is (b) (4) but does have a (b) (4) (b) (4) glycerin (b) (4) purified water plus excipients and drug substances. Typically, if the information provided in support of the container closure components demonstrate that or assure that these components comply with the food contact regulations for packaging materials that could be used with aqueous-based and alcoholic beverages, this would be sufficient to justify the absence of any specific leachables testing (i.e., see 21 CFR 177.1630(g)). If this is not the case, as per ICH Q6A, the applicant will need to provide evidence that leachables levels are sufficiently low (are safe) before dispensing with testing as a stability parameter. The DMF 27314 includes an extractables/leachables report for the container closure system used for the drug product.
- The drug product is *not* packaged with a dose measuring device of any kind. The labeling currently recommends that patients “ask [his/her] pharmacist to give [him/her] a measuring device to help you measure the correct amount of Tuzistra XR.” Other labels and labeling state that an “accurate milliliter measuring device” should be used for dosing. It is recommended that the chemist inform the clinical team of the lack of any co-packaged measuring device for the drug product.

Description of Facility Related Risks or Complexities (i.e. foreign sites, large number of sites involved, etc.)

See EES for complete list of facilities related to this application.

The chlorpheniramine maleate is manufactured (b) (4) (b) (4). The codeine phosphate is manufactured by (b) (4) at their (b) (4). Information for the manufacturer of the drug substances is provided in DMFs referenced in the application. The oral extended release suspension drug product is manufactured by Tris Pharma at their New Jersey facility. This facility was recently evaluated for the SES profile class 21-JAN-2014, and was found to be acceptable.

Biopharmaceutics Filing Review: Summary, Critical Issues and Complexities

Submission: Tris Pharma, Inc. submitted this 505(b)(2) application seeking approval for their codeine polistirex and chlorpheniramine polistirex ER oral suspension (Tuzistra™ XR).

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Drug Product: Tuzistra™ XR is equivalent to (20 mg codeine phosphate/4 mg chlorpheniramine maleate per 5 ml). The reference product for this application is Codeprex™ Pennkinetic®, N021369, UCB Inc. (Codeine Phosphate and Chlorpheniramine Maleate Oral Solution), an immediate release product.

Review: The biopharmaceutics review will focus on the dissolution (b) (4) of this product.

Review Issues Identified: No issues have been identified. Informational reports are being requested.

Recommendation: This NDA is fillable from the Biopharmaceutics perspective.

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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	N/A	Comment
1.	Is the CMC section organized adequately?	X	<input type="checkbox"/>	<input type="checkbox"/>	Information is split between N207768 and DMF 27314 for the drug product
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X	<input type="checkbox"/>	<input type="checkbox"/>	
3.	Are all the pages in the CMC section legible?	<input type="checkbox"/>	<input type="checkbox"/>		All pages examined for production of this IQA were legible.
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	<input type="checkbox"/>	X	<input type="checkbox"/>	No, the strength/established name issue was not addressed.

B. FACILITIES*					
	Parameter	Yes	No	N/A	Comment
5	Is a single, comprehensive list of all involved facilities available in one location in the application?	<input type="checkbox"/>	X	<input type="checkbox"/>	No, but the respective manufacturing sections for the drug substances and drug products contain the site information.
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.	<input type="checkbox"/>	<input type="checkbox"/>	X	Note, however, that it is likely that precursor compounds in the synthesis of codeine are derived from natural sources (e.g., from poppys).

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7	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	<input type="checkbox"/>	X	<input type="checkbox"/>	See above.
8	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X	<input type="checkbox"/>	<input type="checkbox"/>	

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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: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	<input type="checkbox"/>	<input type="checkbox"/>	X	
	1	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	<input type="checkbox"/>	X	<input type="checkbox"/>

* 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	N/A	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X	<input type="checkbox"/>	<input type="checkbox"/>	Exclusion requested as per 21 CFR 25.31(a); Applicant also claims that they know of no extraordinary circumstances regarding the EA.

D. MASTER FILES (DMF/MAF)					
	Parameter	Yes	No	N/A	Comment

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12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X	<input type="checkbox"/>	<input type="checkbox"/>	Refer to table of DMF information above.
-----	---	---	--------------------------	--------------------------	--

E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)					
	Parameter	Yes	No	N/A	Comment
13.	Does the section contain a description of the DS manufacturing process?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Reference is made to DMFs 3885 and 4839. See table above for current review status.
14.	Does the section contain identification and controls of critical steps and intermediates of the DS (in process parameters)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
15.	Does the section contain information on impurities?	X	<input type="checkbox"/>	<input type="checkbox"/>	
16.	Does the section contain information regarding the characterization of the DS?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
17.	Does the section contain controls for the DS?	X	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above; the NDA also contains the specifications for the drug substances by reference to DMF 27314.
18.	Has stability data and analysis been provided for the drug substance?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.
21.	Does the section contain container and closure information?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	See comment for 13 above.

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F. DRUG PRODUCT (DP)					
	Parameter	Yes	No	N/A	Comment
22.	Does the section contain quality controls of excipients?	X	<input type="checkbox"/>	<input type="checkbox"/>	
23.	Does the section contain information on composition?	X	<input type="checkbox"/>	<input type="checkbox"/>	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X	<input type="checkbox"/>	<input type="checkbox"/>	
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	<input type="checkbox"/>	<input type="checkbox"/>	See P.3.4 in DMF 27314.
26.	Is there a batch production record and a proposed master batch record?	X	<input type="checkbox"/>	<input type="checkbox"/>	Yes, see P.3.2 and R.
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X	<input type="checkbox"/>	<input type="checkbox"/>	The P.2 section does include the formulation development history, but it appears that a single formulation was chosen early on and was based on prior knowledge the applicant had with other similar drug products.
28.	Have any biowaivers been requested?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	The biopharmaceutics team have addressed any biowaiver requests (<i>vide infra</i>).
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	X	<input type="checkbox"/>	<input type="checkbox"/>	There is a 16 oz. (b) (4) bottle (b) (4)
30.	Does the section contain controls of the final drug product?	X	<input type="checkbox"/>	<input type="checkbox"/>	As noted above, there is currently no specification parameter for drug product leachables. An evaluation of the extractables/leachables report will be key to determining if such testing should be included as part of the routine stability protocol.

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31.	Has stability data and analysis been provided to support the requested expiration date?	X	<input type="checkbox"/>	<input type="checkbox"/>	As indicated above, the applicant has provided some analyses (plots showing trends) supporting their proposed drug product expiry period.
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	<input type="checkbox"/>	X	<input type="checkbox"/>	The applicant does not appear to be requesting any regulatory relief based on any QbD-related studies.
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	<input type="checkbox"/>	X	<input type="checkbox"/>	

G. METHODS VALIDATION (MV)

	Parameter	Yes	No	N/A	Comment
34.	Is there a methods validation package?	X	<input type="checkbox"/>	<input type="checkbox"/>	See R of DMF 27314. If the reviewer decides that the Agency should evaluate any of the methods, the applicant can be asked to provide sample and reference materials to the Agency laboratory.

H. MICROBIOLOGY

	Parameter	Yes	No	N/A	Comment
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	<input type="checkbox"/>	<input type="checkbox"/>		The microbiology team has been informed of the submission of this application and will make a determination of any review necessary, as per the pilot.

I. LABELING

	Parameter	Yes	No	N/A	Comment
36.	Has the draft package insert been provided?	X	<input type="checkbox"/>	<input type="checkbox"/>	
37.	Have the immediate container and carton labels been provided?	X	<input type="checkbox"/>	<input type="checkbox"/>	
38.	Does section contain tradename and established name?	X	<input type="checkbox"/>	<input type="checkbox"/>	The established name is currently not acceptable as it contains (b) (4)

J. BIOPHARMACEUTICS

	Parameter	Yes	No	Comment
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39.	Does the application contain dissolution data?	X		
40.	Is the dissolution test part of the DP specifications?	X		Codeine: 1 hour (b) (4) % 3 hour (b) (4) % 12 hour NLT (b) (4) % Chlorpheniramine: 1 hour NMT (b) (4) % 3 hour (b) (4) % 12 hour NLT (b) (4) %
41.	Does the application contain the dissolution method development report including data supporting the discriminating ability?	X		“DMF 027314: This DMF includes information such as pharmaceutical development, formulation details, dissolution assay methods and validation, etc.”
42.	Is there a validation package for the analytical method and dissolution methodology?	X		“DMF 027314: This DMF includes information such as pharmaceutical development, formulation details, dissolution assay methods and validation, etc.”
43.	Does the application include a biowaiver request?		X	
44.	Is there information/data supporting the biowaiver request?			N/A
45.	Is there enough information to assess the extended release designation claim?	X		
46.	Does the application include an IVIVC model?	X		No Model: But IVIVC report contains diss graph only; no correlation graphs ie, AUC/Cmax vs % Diss or in vivo-diss, etc.
47.	Does the application include information/data on in vitro alcohol dose-dumping potential?	X		“An in vitro dissolution study to evaluate the effect of alcohol on the drug release profile showed that concentrations of alcohol greater than or equal to 40% (v/v) may have some impact on accelerating the release of Codeine from the formulation (with little to no impact on chlorpheniramine release).”
48.	Is there any in vivo BA or BE information in the submission?	X		As part of the (b) (4) two studies are conducted for the (b) (4) (300116 and 300117).
49.	Is there any design space proposed using in vitro release as a response variable?		X	

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50.	Is the control strategy related to in vitro drug release?	X		
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A. FILING CONCLUSION					
	Parameter	Yes	No	N/A	Comment
51.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X	<input type="checkbox"/>	<input type="checkbox"/>	
52.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	<input type="checkbox"/>	<input type="checkbox"/>	X	
53.	Are there any potential review issues identified?	<input type="checkbox"/>	X	<input type="checkbox"/>	
54.	Are there any comments to be sent to the Applicant as part of the 74-Day letter?				1). Please provide detailed report of dissolution method validation. 2). Please provide detailed report of the ^{(b) (4)} model development.
55.	Are there any internal comments to other disciplines:			X	

REVIEW AND APPROVAL

This document will be signed in DARRTS by the following:

Craig M. Bertha, PhD, Acting CMC Lead
Assadollah Noory, PhD, Biopharmaceutics Reviewer
Tapash Ghosh, PhD., Biopharmaceutics Team Leader
Eric Duffy, PhD, Division Director (DNDQA III)

{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/

CRAIG M BERTHA
08/13/2014

ASSADOLLAH NOORY
08/13/2014

TAPASH K GHOSH
08/13/2014

ERIC P DUFFY
08/14/2014