CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204078Orig1s000

<u>CHEMISTRY REVIEW(S)</u>

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 204078/000	**Action Goal:**	
S' ate:	31-JUL-2012	**District Goal:**	01-APR-2013
Re .ory:	31-MAY-2013		
Applicant:	ECLAT PHARMS	**Brand Name:**	(b) (4)
	1129 20TH ST NORTHWEST STE 600	**Estab. Name:**	
	WASHINGTON, DC 20036	**Generic Name:**	
Priority:	5	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	170	001; INJECTION; NEOSTIGMINE METHYLSULFATE; 1MG/1ML 002; INJECTION; NEOSTIGMINE METHYLSULFATE; .5MG/1ML	

Application Comment:

FDA Contacts:	L. RIVERA	Product Quality PM	3017964013
	A. MEYER	Regulatory Project Mgr	3017961258
	D. CHRISTODOULOU	Team Leader	3017961342

Overall Recommendation:	ACCEPTABLE	on 31-JAN-2013	by T. SHARP	()	3017963208
	PENDING	on 10-AUG-2012	by EES_PROD		
	PENDING	on 10-AUG-2012	by EES_PROD		

Reference ID: 3323196

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: USP TESTING (on 10-AUG-2012 by L. RIVERA () 3017964013)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	10-AUG-2012				RIVERAL
SUBMITTED TO DO	16-AUG-2012	Product Specific			STOCKM
UNDER REVIEW	03-SEP-2012				BRYKMANR
FOREIGN AGENCY EIR RECEIVED ON 29MAY2012 FOR REVIEW OF CTL PROFILE.					
ASSIGNED INSPECTION TO IB	01-OCT-2012	Product Specific			BRYKMANR
INSPECTION SCHEDULED	30-NOV-2012		(b) (4)		IRIVERA
INSPECTION PERFORMED	(b) (4)		(b) (4)		Mark.Parmon
See Hard Copy EIR					
DO RECOMMENDATION	30-JAN-2013			ACCEPTABLE	PHILPYE
				INSPECTION	
OC RECOMMENDATION	31-JAN-2013			ACCEPTABLE	SHARPT
				DISTRICT RECOMMENDATION	

Reference ID: 3323196

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment Comment: MANUFACTURE, CONTROL, PACKAGING, TESTING, LABELING AND STABILITY TESTING (on 10-AUG-2012 by L. RIVERA () 3017964013)

Profile: (b) (4) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	10-AUG-2012				RIVERAL
SUBMITTED TO DO	16-AUG-2012	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	19-AUG-2012	GMP Inspection			PHILPYE
UNDER REVIEW	26-SEP-2012				STOCKM
CASE ID (b) (4) IN QUEUE FOR REVIEW; CSO NOT YET ASSIGNED					
DO RECOMMENDATION	11-JAN-2013			ACCEPTABLE	PHILPYE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	17-JAN-2013			ACCEPTABLE	SHARPT
				DISTRICT RECOMMENDATION	

Reference ID: 3323196

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE RELEASE TESTER

Establishment Comment: RELEASE TESTING, MANUFACTURE, ANALYZE AND RELEASE THE API (on 10-AUG-2012 by L. RIVERA () 3017964013)

Profile: STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				**Reason**	
SUBMITTED TO OC	10-AUG-2012				RIVERAL
SUBMITTED TO DO	14-AUG-2012	GMP Inspection			STOCKM
INSPECTION SCHEDULED	03-SEP-2012		(b) (4)		BRYKMANR
DO RECOMMENDATION	31-DEC-2012			ACCEPTABLE	BRYKMANR
PREVIOUS FDA INSPECTION ENDING ON (b) (4) COVERED THE SAME PROFILE WITH A FINAL CLASSIFICATION OF VAI.				BASED ON FILE REVIEW	
OC RECOMMENDATION	31-DEC-2012			ACCEPTABLE	SAFAAIJAZIR
				DISTRICT RECOMMENDATION	

Reference ID: 3323196

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/s/

MARY GRACE LUBAO
06/11/2013

Chemistry Review Cover Sheet

NDA 204078

(b) (4)

(NEOSTIGMINE METHYLSULFATE INJECTION)

Arthur B. Shaw, Ph.D.

DNDQA III/Branch VIII/DAAAP

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Reference ID: 3297724

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Reference ID: 3297724

Chemistry Review Data Sheet

1. NDA 204078
2. REVIEW #:1
3. REVIEW DATE: April 26, 2013
4. REVIEWER: Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

Document	Document Date	Comment
Original	2012-07-31	
Micro IR	2012-8-28	Not in DARRTS. Request for Process Validation
Amendment	2012-09-13	Response to micro IR
Filing review CMC	2012-09-28	Fileable
Filing review Micro	2012-09-17	Fileable
Filing Issues Letter	2012-10-12	Fileable Micro issues identified
Amendment	2012-11-15	Response to filing issues letter
Micro IR	2012-11-30	Not in DARRTS. Additional Micro requests
Amendment	2012-12-28	Response to 11/30 micro IR
Micro IR	2013-01-08	Additional micro issues
CMC IR	2013-01-13	Numerous issues
Micro amendment	2013-01-18	Response to 01/08 IR
Micro review	2013-01-25	Recommend Approval
CMC Amendment	2013-02-07	Response to 1/13 IR letter
CMC Amendment	2013-02-13	Update Stability
Labeling amendment	2013-02-13	
CMC IR	2013-02-15	Revise P.5 to include spec for leachables
CMC Amendment	2013-02-21	Response to 2/15 IR letter
CMC IR	2013-02-27	E-mail not in DARRTS Request proof of structure of leachable.
CMC IR	2013-02-28	E-mail not in DARRTS
CMC IR	2013-03-04	Request amendment for DMF (b) (4) Request info for large peak in test for related substances
CMC Amendment	2013-03-07	Response to 2/27 and 2/28 IR emails
CMC IR	2013-03-13	Numerous issues
CMC Amendment	2013-03-18	Response to 3/04 IR letter
Labeling IR	2013-03-26	Request for revised carton and container labels
Labeling Amendment	2013-04-01	Revised carton and container labels
CMC Amendment	2013-04-10	Response to 3/13 IR letter
CMC Amendment	2013-04-22	Remaining response to 2013-01-13

7. NAME & ADDRESS OF APPLICANT:

Reference ID: 3297724

Éclat Pharmaceuticals
699 Trade Center Blvd, Suite A
Chesterfield, MO 63005

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Proposed: (b) (4)
   b) Non-Proprietary Name (USAN): Neostigmine methylsulfate
   c) Code Name/# P404 Note that this code will be used a number of times in the review since that is the name used by the applicant when referring to the active substance in the drug product
   d) Chem. Type/Submission Priority
      - Chem. Type: 5 (new formulation and manufacturer) and 7)marketed unapproved drug) (NDA 654 for Prostigmin (neostigmine) Ophthalmic Injection was approved in 1939 and withdrawn in 1996)
      - Submission Priority: S

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

10. PHARMACOL. CATEGORY: parasympathomimetic agent that acts as a reversible acetylcholinesterase inhibitor (anti-cholinesterase).

11. DOSAGE FORM: Solution; injection

12. STRENGTH/POTENCY: 0.5 and 1 mg/mL

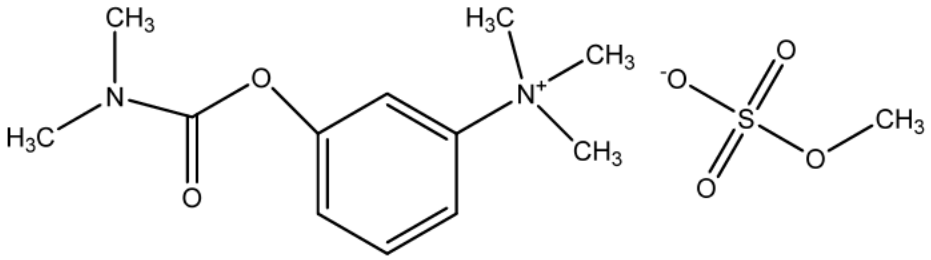
13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No

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

Benzenaminium, 3-[[(dimethylamino)carbonyl]oxy]-N,N,N-trimethyl-, methyl sulfate.



$C_{13}H_{22}N_2O_6S$ 334.39

CAS RN 51-60-5

Reference ID: 3297724

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED
(b) (4)			Neostigmine methylsulfate	Adequate	12/21/2012
			(b) (4)	Adequate	04/01/2013
				No review per MAPP 5015.5 USP statement in P.7	

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	1/31/2013	
EA	Categorical Exclusion granted		
Microbiology	Adequate	1/25/2013	E. Pfeiler
Statistics	Not needed		

Reference ID: 3297724

The Chemistry Review for NDA 200436

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application may be approved from a CMC point of view.

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

1. We remind you that you must submit a PAS if the drug substance supplier [redacted] (b) (4).
2. We recommend making [redacted] (b) (4) a Critical Process Parameter.
3. We recommend amending the manufacturing directions in the master batch record to do the following:
   a) Include [redacted] (b) (4)
   b) Include [redacted] (b) (4)

II. Summary of Chemistry Assessments

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

1. Drug Substance

The drug substance is a white, crystalline powder, freely soluble in water. It is covered by USP and EP monographs. It is a parasympathomimetic agent that acts as a reversible anticholinesterase inhibitor. Complete CMC information is included in DMF [redacted] (b) (4) which was found acceptable in a review dated December 21, 2012 by Dr. Edwin Jao. The applicant performs their own testing for the receipt of the drug substance and the methods have been validated. The applicant has provided the synthetic procedure from the DMF holder, [redacted] (b) (4) which shows that a known [redacted] (b) (4) [redacted] We recommend that the applicant commit to submit a Prior Approval Supplement if the DMF holder [redacted] (b) (4) The DMF holder controls this compound at a level of [redacted] (b) (4) in the finished drug substance and includes the amounts in their COA. This has been found acceptable by the pharm/tox team. All other impurities are well-controlled and present no safety issues. The drug substance is stable.

2. Drug Product

The drug product is a sterile, non-pyrogenic solution. There is a USP monograph for neostigmine methylsulfate injection and the product has been marketed without an NDA for many years. However there was an NDA for the same drug substance (NDA 654, Prostigmine Ophthalmic Solution) which was approved in 1939 and withdrawn in 1996. Therefore this has the Chemical Classification of 7 and 5. It is intended as a multi-use vial containing 10 mL of

Reference ID: 3297724

drug product at either 0.5 mg/mL or 1.0 mg/mL. The proposed dosing is 30 µg/kg. Additional doses, up to a total dose of 70 µg/kg (or 5 mg, whichever is less), may be given. Since this is a multi-use vial, phenol is added as a preservative (b) (4) In the Pharmaceutical Development (PD) report the applicant provided data to justify the choice of this preservative compared with others, (b) (4) The PD report also contains a study showing that (b) (4) causes degradation of the drug product and therefore the product is (b) (4). The entire Microbiology package, including the preservative effectiveness testing and the (b) (4) procedure, were found adequate in the Microbiologist's review dated 1/25/2013.

The solution is (b) (4) stoppers, which are supplied (b) (4) The stoppers are covered in DMF (b) (4) which was found adequate.

The applicant evaluated extractables and potential leachables in the PD report and found one potential leachable, (b) (4) whose structure was confirmed by mass spectrometry. The applicant developed an assay to be used in stability studies for the compound, with an acceptance criterion of NMT (b) (4) which is the limit of quantitation. This level was found acceptable by the pharm/tox review team.

The drug product specifications are adequate to control the potency, impurities and microbiological quality. The applicant has provided sufficient stability data to support a 24 month expiration date.

The drug is stable when stored at (b) (4) for up to 12 months, which permits an expiration date of 24 months.

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

The drug product is used during surgery to reverse the effects of neuromuscular blocking agents (NMBAs) used during general anesthesia. The drug product has been marketed as an unapproved product for many years. The drug product is labeled to be injected intravenously as a bolus over one minute at an initial dose of 30 µg/kg. Additional doses up to 70 µg/kg (or 5 mg total, whichever is smaller) may be given.

C. Basis for Approvability or Not-Approval Recommendation

The quality of the drug product is adequately controlled, from the synthesis of the drug substance through the specifications and stability of the drug product, to support its intended use. Inspections are satisfactory.

III. Administrative

A. Reviewer's Signature See DARRTS

B. Endorsement Block: See DARRTS

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/s/

ARTHUR B SHAW
04/26/2013

PRASAD PERI
04/26/2013
I concur

Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER:204-078

2. SUBMISSION TYPE :Original

3. SUBMISSION NUMBER:000

4. PRODUCT PROPERTIES:

Trade or Proprietary Name:	[redacted] (b) (4)
Established or Non-Proprietary Name (USAN):	Neostigmine methyl sulfate
Dosage Form:	Injection

5. NAME & ADDRESS OF APPLICANT:

Name:	Eclat Pharmaceuticals
Address:	699 Trade Center Bild, Suite A, Chesterfield, MO 63005
Representative:	Lauren H. Wind, Senior Consultant, The Weinberg Group

6. SUBMISSION PROPERTIES:

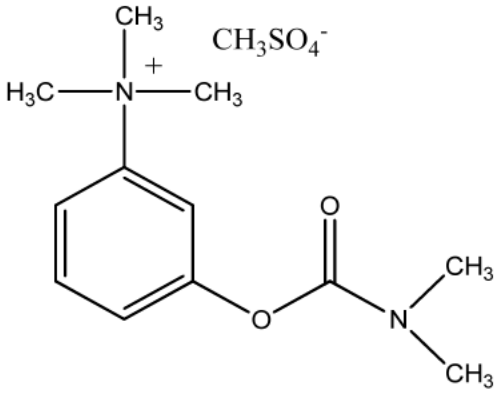
Review Priority :	Standard
Classification (Code):	2S
Property (Legal Basis):	505 (b) 2
Responsible Organization:	OND

Reference ID: 3197245

Review Information

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

Chemical Name(s): (m-hydroxyphenyl) trimethylammonium methylsulfate dimethylcarbamate;
Benzenamimium, 3[[(dimethylamino) carbonyl]oxy]-N,N,N-trimethyl-,methylsulfate
Molecular formula: C13H22N2O6S
Molecular weight: 334.40
CAS Registry Number: [51-60-5]



2. INDICATION: Reversal of the effects of nondepolarizing neuromuscular blocking agents after surgery

3. PHARMACOLOGICAL CATEGORY:Acetylcholine esterase inhibitor,

Reference ID: 3197245

4. ROUTE OF ADMINISTRATION:Intravenous Injection

5. STRENGTH/POTENCY:1 mg/mL ; 0.5 mg/mL

6. Rx/OTC DISPENSED: ☒Rx ☐OTC

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

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

Reference ID: 3197245

8. RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
[redacted] (b) (4)			Drug Substance	February 23, 2012	None
			[redacted] (b) (4)	April 17, 2012	None
				April 12, 2012	None

b. Consults Recommended by CMC and Biopharmaceutics

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	☐	☐	
Clin Pharm	☒	☐	
EES	☒	☐	
Pharm/Tox	☒	☐	
Methods Validation	☐	☒	
EA	☒	☐	
New Drug Micro	☒	☐	
CDRH	☐	☐	
Other	☐	☐	

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

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
[redacted] (b) (4)			
PIND		111853	Cross referenced in form 356h
NDA		20-624 Anzemet	Cross referenced in form 356h
NDA		20-551	Cross referenced in form 356h

Reference ID: 3197245

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

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
PIND		111853	All pre IND and pre NDA communications

Overall Conclusions and Recommendations

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	CMC Filing Issues
☐	☒	1. Only 6 month stability data 2. Only one leachable testing point However due to the medical necessity of this drug product the division decided to file this application and the above deficiencies are not major filing issues.

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
☒	☐	• Provide updated stability data including leachables.

Is the Product Quality Section of the application fileable from a biopharmaceutics perspective?		
Yes	No	Biopharmaceutics Filing Issues
☒	☐	None

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
☐	☒	None

Reference ID: 3197245

Summary and Regulatory History:

The application is submitted as a 505(b)(2), based on the approved NDA 00-654, Prostigmine (neostigmine bromide) ophthalmic solution, held by Roche and later discontinued.
NDA 00-654 was approved in 1939. The Original submission was DESI designated. This file obtained from the document room labeled as 'Historical Document' contains correspondence from 1939 up to July 23, 1971. This file contains document which references the following NDAs with prostigmine in combination with other drug moieties. NDA 02-574 (Prostigmine & Morphine hypodermic tablets for solution and injection, NDA 02-575 (Prostigmine & Pantopan mixed alkaloids of Opium) hypodermic tablets for solution and injection, [redacted] (b) (4), NDA 02-449 (Prostigmine & Atropine) ampoule for injection. All these products appear to have been withdrawn from the market. The structure of the drug substance presented in this historical file is the same as that of the API of this new NDA. This drug product appears to have been in the market since the nineteen seventies. Based on its regulatory history, the API in this NDA is <u>not a New Molecular Entity.</u>

This is a marketed unapproved product, by APP and is formulated with [redacted] (b) (4) phenol, sodium acetate, [redacted] (b) (4), sodium hydroxide, water for injection and [redacted] (b) (4) in 10 mL vials in two strengths (0.5 mg/mL and 1.0 mg/mL). The applicant has not requested for a waiver of *in vivo* bioequivalence and does not apply to this NDA. The applicant refers to published litereature for human Pk data and the Office of Clinical Pharmacology will evaluate this information for its acceptability.
The proposed drug product will be marketed [redacted] (b) (4)

Currently, [redacted] (b) (4)

Reference ID: 3197245

CMC Summary:
Critical Issues and Complexities

CMC Critical Issues or Complexities

- **The drug substance manufacturer** [redacted] (b) (4) **is the** [redacted] (b) (4) (b) (4) (b) (4)
- **The drug product formulation is** [redacted] (b) (4)
- **The applicant has provided only six month stability data.**
- **There is only one leachable testing point at six months. A PMR may be necessary to evaluate the stability and leachables of the drug product.**
- **No obvious review issues were identified based on this submission.**
- **The proposed facilities were submitted for CGMP compliance and scheduled for inspection.**
- **The extractables data provided were agreed upon during the PIND meetings. Refer to meeting minutes in DARRTS.**

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
☐	☒	

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

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

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

Reference ID: 3197245

Biopharmaceutics Summary:
Critical Issues, Complexities, and Consults

Critical Issues or Complexities
Not applicable. Please refer filing review by Dr. Elsbeth Chikale in DARRTS dated 09/11/2012

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?	☒	☐	
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	☒	☐	
3.	Are all the pages in the CMC section legible?	☒	☐	
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	☒	☐	

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

Reference ID: 3197245

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.**	☐	☐	Not Applicable
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)	☒	☐	

Reference ID: 3197245

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)	☒	☐	
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)	☒	☐	
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	☐	☒	May not be a filing issue

* 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

Reference ID: 3197245

	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	

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?	☒	☐	*See table on cover page.*

E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
13.	Does the section contain a description of the DS manufacturing process?	☒	☐	DMF has been referenced
14.	Does the section contain identification and controls of critical steps and intermediates of the DS(in process parameters?	☒	☐	DMF has been referenced
15.	Does the section contain information on impurities?	☒	☐	DMF has been referenced
16.	Does the section contain information regarding the characterization of the DS?	☒	☐	DMF has been referenced
17.	Does the section contain controls for the DS?	☒	☐	DMF has been referenced
18.	Has stability data and analysis been provided for the drug substance?	☒	☐	DMF has been referenced
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	☐	☒	
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	☐	☒	
21.	Does the section contain container and closure information?	☒	☐	DMF has been referenced

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F. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
22.	Does the section contain quality controls of excipients?	☒	☐	
23.	Does the section contain information on composition?	☒	☐	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	☒	☐	
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?	☒	☐	
26.	Is there a batch production record and a proposed master batch record?	☒	☐	
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	☐	☒	
28.	Have any biowaivers been requested?	☐	☒	
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	☒	☐	
30.	Does the section contain controls of the final drug product?	☒	☐	
31.	Has stability data and analysis been provided to support the requested expiration date?	☒	☐	
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	☐	☒	
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	☐	☒	

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

H. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	☐	☒	Microbiologist has requested the validation data.

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
36.	Has the draft package insert been provided?	☒	☐	
37.	Have the immediate container and carton labels been provided?	☒	☐	
38.	Does section contain tradename and established name?	☒	☐	Trade has been proposed and is being reviewed by DMEPA

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J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
39.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	☒	☐	
40.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	☐	☒	
41.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	☒	☐	• Updated stability data including leachable data has been requested

REVIEW AND APPROVAL

This document will be signed in DARRTS by the following:

CMC Lead Dr. Ramesh Raghavachari
Branch Chief Dr. Peri Prasad

{See appended electronic signature page}

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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/

RAMESH RAGHAVACHARI
09/28/2012

PRASAD PERI
09/28/2012
I concur