CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206610Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 206610
Assessment 8

Drug Product Name	Acetaminophen for Injection
Dosage Form	Intravenous injection
Strength	10 mg/mL
Route of Administration	intravenous
Rx/OTC Dispensed	Rx
Applicant	Mylan Laboratories Limited
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document #34; eCTD0033	10 Jul 2019	Facilities

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	-	-
Drug Product	-	-
Manufacturing	Christina Capacci Daniel	Christina Capacci Daniel
Microbiology	-	-
Biopharmaceutics	-	-
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	-	-
Environmental	-	-

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

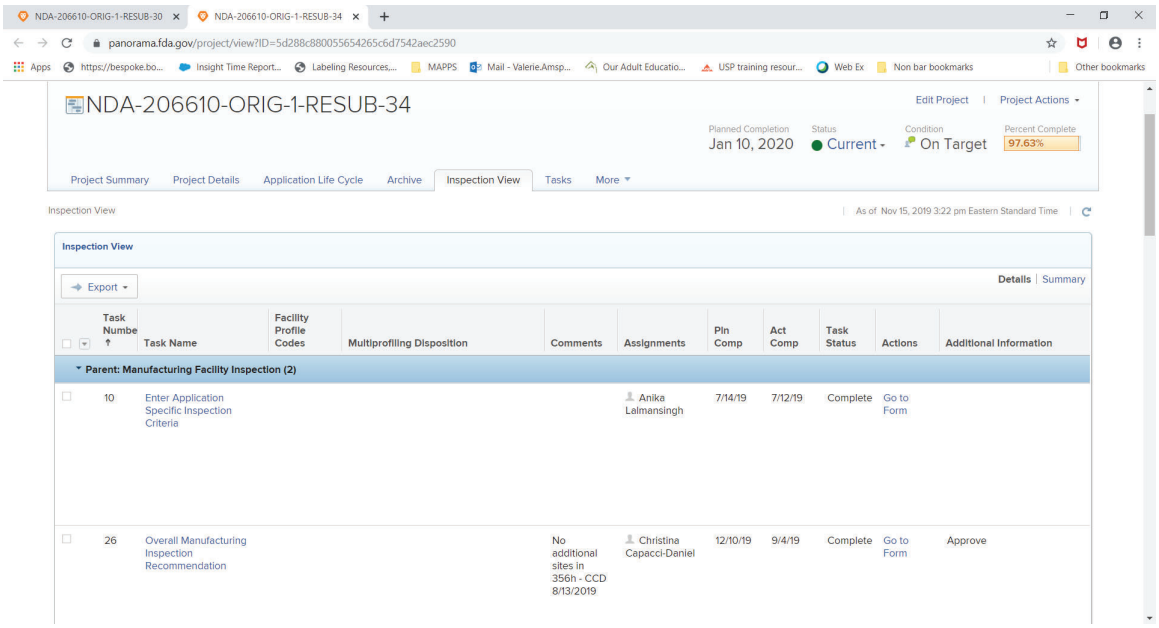
CMC recommends approval. The previous recommendation of complete response was due to an inspection (May 2019) resulting in a change in facility status to Potential Official Action Indicated.
The facility issues have been resolved and the Office of Pharmaceutical Manufacturing Assessment (OPMA) (formerly OPF) now recommend approval. See screenshot from Panorama at the bottom of this page.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

This is review #8. The previous review in April 2019 recommended approval however an inspection (May 2019) resulted in a change in facility status to Potential Official Action Indicated and an addendum in May 2019 recommended complete response.
No other CMC discipline reviewed any information in this resubmission. Only the facilities reviewer looked at the status of the manufacturing facility and determined that OPMA recommends approval.

Proposed Indication(s) including Intended Patient Population	Indicated for the management of moderate to severe pain with adjunctive opioid analgesics; Indicated for the reduction of fever.
Duration of Treatment	N/A
Maximum Daily Dose	4 grams daily
Alternative Methods of Administration	N/A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NDA-206610-ORIG-1-RESUB-34
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Project Actions
Planned Completion
Jan 10, 2020
Status
Current
Condition
On Target
Percent Complete
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Project Summary
Project Details
Application Life Cycle
Archive
Inspection View
Tasks
More
Inspection View
As of Nov 15, 2019 3:22 pm Eastern Standard Time
Inspection View
Export
Details | Summary
Task Numbe
Task Name
Facility Profile Codes
Multiprofiling Disposition
Comments
Assignments
Pin Comp
Act Comp
Task Status
Actions
Additional Information
Parent: Manufacturing Facility Inspection (2)
10
Enter Application Specific Inspection Criteria
Anika Lalmansingh
7/14/19
7/12/19
Complete
Go to Form
26
Overall Manufacturing Inspection Recommendation
No additional sites in 356h - CCD 8/13/2019
Christina Capacci-Daniel
12/10/19
9/4/19
Complete
Go to Form
Approve

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VALERIE R AMSPACHER
01/21/2020 10:28:18 AM

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

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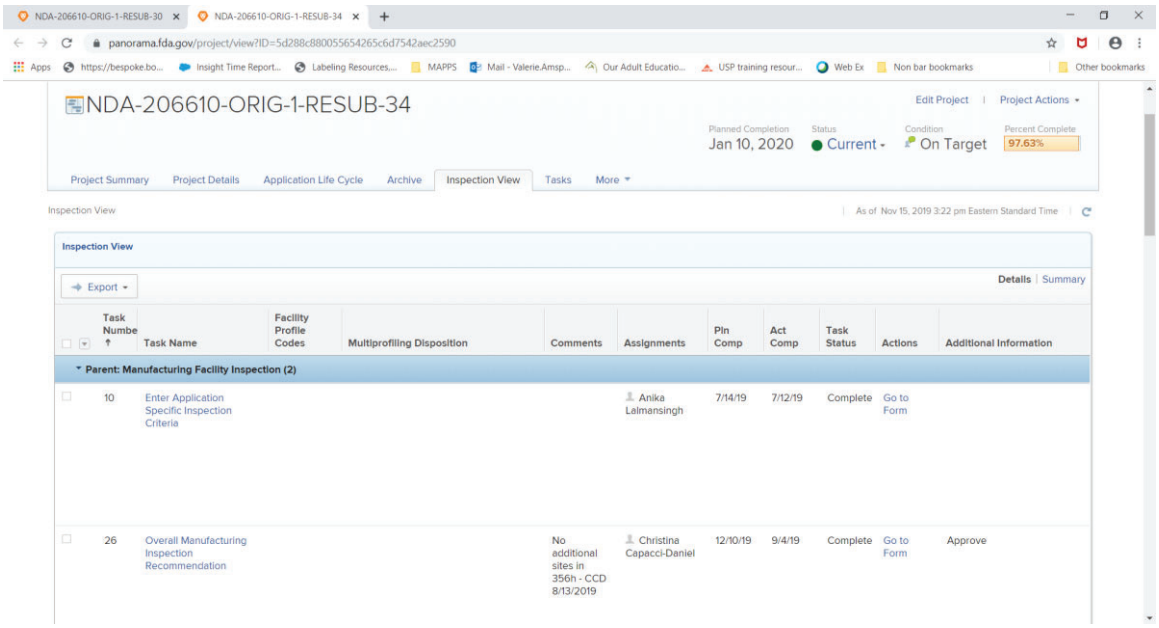
Alternative Methods of Administration	N/A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Application Life Cycle
Archive
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Tasks
More
Inspection View
As of Nov 15, 2019 3:22 pm Eastern Standard Time
Inspection View
Export
Details | Summary
Task Number
Task Name
Facility Profile Codes
Multiprofiling Disposition
Comments
Assignments
Pln Comp
Act Comp
Task Status
Actions
Additional Information
Parent: Manufacturing Facility Inspection (2)
10
Enter Application Specific Inspection Criteria
Anika Lalmansingh
7/14/19
7/12/19
Complete
Go to Form
26
Overall Manufacturing Inspection Recommendation
No additional sites in 356h - CCD 8/13/2019
Christina Capacci-Daniel
12/10/19
9/4/19
Complete
Go to Form
Approve

Valerie Amspacher

Digitally signed by Valerie Amspacher
Date: 11/18/2019 01:25:21PM
GUID: 5714dbd10078d2d3d9b60a0ceb819fc3

Julia Pinto

Digitally signed by Julia Pinto
Date: 11/19/2019 05:49:55PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

Executive Summary

I. Recommendations and Conclusion on Approvability

CMC recommends complete response due to a withhold recommendation from OPF for the Mylan Laboratories Ltd. (FEI 3007648351) manufacturing facility for this application.

II. Summary of Quality Assessments

A. Product Overview

This is CMC Review #7 reviewing Supporting Document # 30; eCTD # 0029 (response to complete response letter dated 6 Dec 2017). It is an addendum to Review #6. This review recommends complete response due to a withhold recommendation from OPF.

Regulatory History

CMC Review #6 dated 29 Apr 2019 reviewed Supporting Document # 30; eCTD # 0029 (response to complete response letter dated 6 Dec 2017). The recommendation as of 29 Apr 2019 was for approval, however a recent inspection resulted in change in facility status to Potential Official Action Indicated therefore this addendum is added to Review #6.

CMC Review #5 dated 7 Nov 2017 reviewed Supporting Document # 21; eCTD # 0020 (response to complete response letter dated 1 Feb 2017). Recommended approval.

CMC Review #4 dated 26 Jan 2017 reviewed Supporting Document # 16; eCTD # 0015 (response to complete response letter dated 10 Mar 2016). Recommended approval.

CMC Review #3 dated 4 Mar 2016 reviewed Supporting Document #13; eCTD # 0012 (response to complete response letter dated 1 Mar 2015). It recommended a complete response due to the sponsor not completing an extraction study to, "identify the extractables from (b) (4) extraction study and determine if they are present in the drug product formulation." Facilities also had a withhold recommendation.

CMC Review #1 and 2 dated 3 and 26 Feb 2015 reviewed the original NDA as submitted on 3 May 2014. It recommended a complete response due to up to (b) (4) mcg of unidentified material (b) (4) as well as a withhold recommendation from facilities.

Proposed Indication(s) including Intended Patient Population	***Indicated for the management of moderate to severe pain with adjunctive opioid analgesics; Indicated for the reduction of fever.***
Duration of Treatment	***N/A***
Maximum Daily Dose	***4 grams daily***
Alternative Methods of Administration	***N/A***

B. Quality Assessment Overview

OPF has issued a withhold for the Mylan Laboratories Ltd. (FEI 3007648351) manufacturing facility for this application. In an email dated 20 May 2019 facilities reviewer Christina Capacci-Daniel states, "During a recent inspection of the Mylan Laboratories Ltd. (FEI 3007648351) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved."

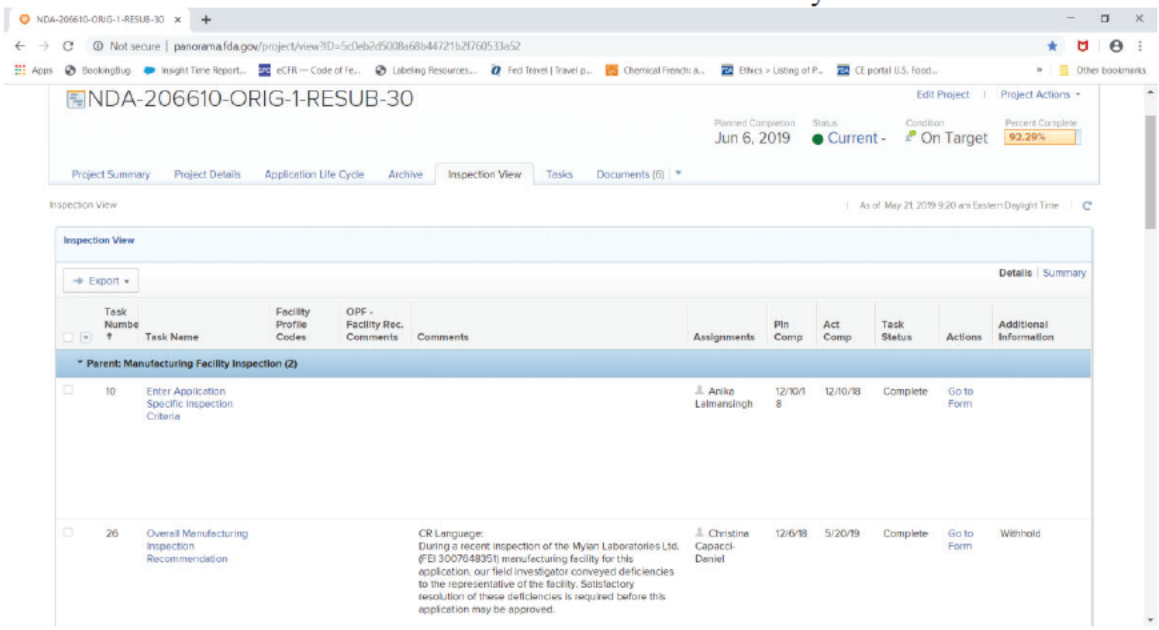
C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

See Review #6

Screenshot of facilities withhold recommendation taken 21 May 2019.



NDA-206610-ORIG-1-RESUB-30

Edit Project | Project Actions

Planned Completion: Jun 6, 2019 | Status: Current - | Condition: On Target | Percent Complete: 92.29%

Project Summary | Project Details | Application Life Cycle | Archive | Inspection View | Tasks | Documents (6)

Inspection View

As of: May 21, 2019 9:20 am Eastern Daylight Time

Inspection View

Export | Details | Summary

Task Number	Task Name	Facility Profile Codes	OPF - Facility Rec. Comments	Comments	Assignments	Pln Comp	Act Comp	Task Status	Actions	Additional Information
Parent: Manufacturing Facility Inspection (2)										
10	Enter Application Specific Inspection Criteria				Anike Lelmansingh	12/10/18	12/10/18	Complete	Go to Form	
26	Overall Manufacturing Inspection Recommendation			CR Language: During a recent inspection of the Mylan Laboratories Ltd. (FEI 3007648351) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.	Christine Capacci-Daniel	12/6/18	5/20/19	Complete	Go to Form	Withhold

Valerie Amspacher

Digitally signed by Valerie Amspacher
Date: 5/21/2019 05:01:39PM
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Julia Pinto

Digitally signed by Julia Pinto
Date: 5/22/2019 10:58:35AM
GUID: 5050dbcb00001294a888a4bdc20a3a58

NDA 206610 Resubmission, Acetaminophen Quality Assessment

Table of Contents

Executive Summary

I. Recommendations and Conclusion on Approvability

CMC recommends approval. The sponsor has changed (b) (4) and they have completed the appropriate studies expected when there is a change of (b) (4). The change in (b) (4) is in response to a Pharm/tox request to perform toxicology studies on the (b) (4) registered in previous submissions.
The shelf life of the lyophilized powder is 24 months at 20°C to 25°C (68°F to77°F). The solution is stable for 12 hours at 20°C to 25°C.

II. Summary of Quality Assessments

A. Product Overview

This is CMC Review #6 reviewing Supporting Document # 30; eCTD # 0029 (response to complete response letter dated 6 Dec 2017). This review recommends approval.

Regulatory History

CMC Review #5 dated 7 Nov 2017 reviewed Supporting Document # 21; eCTD # 0020 (response to complete response letter dated 1 Feb 2017). Recommended approval.

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CMC Review #1 and 2 dated 3 and 26 Feb 2015 reviewed the original NDA as submitted on 3 May 2014. It recommended a complete response due to up to (b) (4) of unidentified material in (b) (4) as well as a withhold recommendation from facilities.

Proposed Indication(s) including Intended Patient Population	***Indicated for the management of moderate to severe pain with adjunctive opioid analgesics; Indicated for the reduction of fever.***
Duration of Treatment	***N/A***
Maximum Daily Dose	***4 grams daily***
Alternative Methods of Administration	***N/A***

B. Quality Assessment Overview

Drug Product and Microbiology reviews were completed in this review cycle. All recommend approval. Also, see screenshot of facility approval at the end of this executive summary.
The sponsor changed (b) (4) This is a significant change because the drug product is a (b) (4) lyophilized powder for intravenous use.
The sponsor performed adequate leachables/drug loss studies (b) (4)

They also performed adequate microbiology studies showing validation of the drug product (b) (4) the lyophilization process. Validation of the (b) (4) of the components of the container closure system was also shown to be adequate.

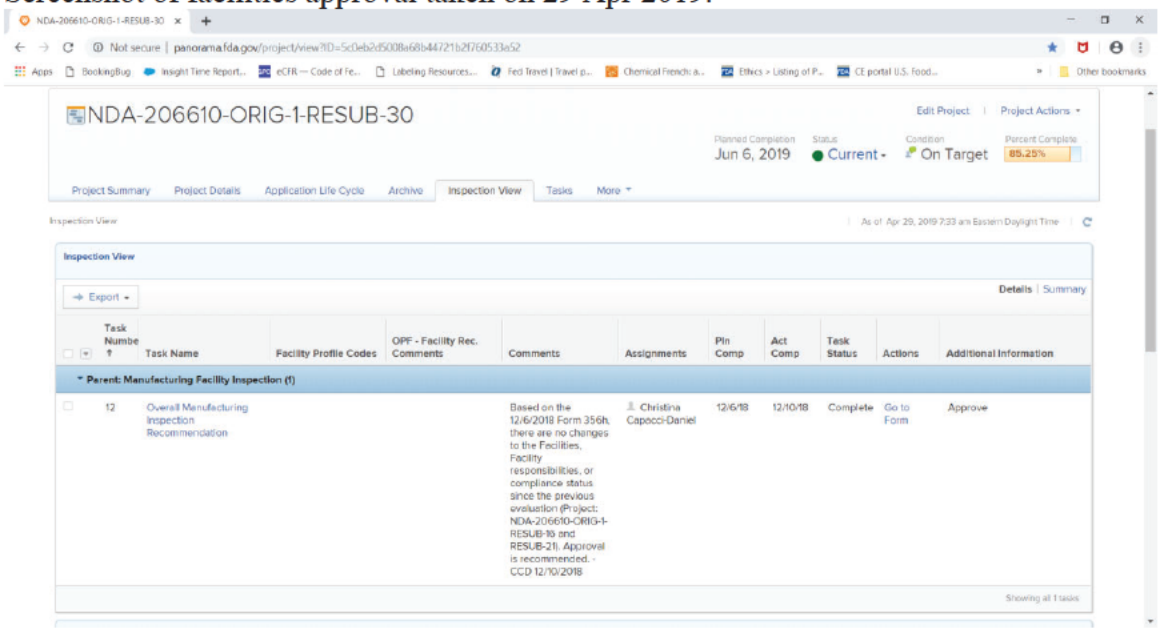
C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

See attachement

Screenshot of facilities approval taken on 29 Apr 2019.



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Julia Pinto

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Date: 4/29/2019 11:10:26AM
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MICROBIOLOGY

Product Background: The drug product is a [redacted] (b) (4) lyophilized powder indicated for the treatment moderate pain and fever reduction.

NDA: 206610 (CR Response)

Drug Product Name / Strength: Acetaminophen / 1 g/vial

Route of Administration: IV

Applicant Name: Mylan Laboratories Limited

Manufacturing Site:
Mylan Laboratories Limited (Specialty Formulation Facility)
19-A, Plot No. 284-B/1
Bommasandra Jigani Link Road
Industrial Area, Anekal Taluk
Bangalore, Karnataka, India 560105

Method of Sterilization: [redacted] (b) (4)

Review Recommendation: Adequate

Review Summary: Drug product is [redacted] (b) (4) and lyophilized. This review covers the validation of [redacted] (b) (4) and sterilization of related components.

List Submissions Being Reviewed:
05/05/2014
12/06/2018

Highlight Key Outstanding Issues from Last Cycle: See "Remarks" below.

Remarks: The original submission for this application was received 05/05/2014 and was reviewed and found adequate for Microbiology on 02/18/2015. However, the applicant was issued a Complete Response letter by the Agency dated 02/27/2015. A second Complete Response letter was issued 12/06/2017. The subject submission contains [redacted] (b) (4) validation information for equipment which has been installed/upgraded since the original Microbiology review was performed (See "Note to Reviewer" below).

Concise Description Outstanding Issues Remaining: NA

Supporting Documents: N206610R1.doc, dated 18 February 2015, reviewed the original NDA submission with a recommendation of "Adequate."

List Number of Comparability Protocols (ANDA only): N/A

Note to Reviewer – The original submission was reviewed and found adequate in N206610R1.doc, dated 18 February 2015. Drug product is manufactured (b) (4) of the proposed manufacturing facility. The applicant states that there have been no changes to the overall manufacturing process, but (b) (4) has been refurbished since the original submission, with several new pieces of equipment installed and upgrades performed to some existing equipment. No changes are reported for manufacturing equipment used in (b) (4) Additionally, no changes are reported for the drug product formulation, batch size, container-closure system, release/stability specifications, analytical methods or labeling. (b) (4) This review will cover only those sections for which changes have been reported.

P. 3.5 Process Validation and/or Evaluation

(b) (4) ***Manufacturing Process***

(b) (4)

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Jason God

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Date: 1/18/2019 10:22:04AM
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Denise Miller

Digitally signed by Denise Miller
Date: 1/18/2019 10:42:17AM
GUID: 508da7280002a5d546459b998253d1aa

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
	II	(b) (4)	(b) (4)	Adequate	11/17/2014	
	III			Adequate	11/22/2014	
	III			Adequate	11/22/2014	
	III			Adequate	11/22/2014	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22450	Listed drug product that is the basis for submission. Held by Cadence Pharmaceuticals Inc.

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

Valerie Amspacher

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Date: 4/29/2019 07:44:45AM
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Julia Pinto

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Date: 4/29/2019 11:09:42AM
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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	Formulation Container Closure Process Parameters Scale/Equipment/ Site	High	Drug product release specification includes sterility (USP <71>) and bacterial endotoxin (USP <85>) testing. Container closure integrity studies indicate that the container closure system remains integral and therefore can maintain the sterility of the product.	Acceptable	Given that the product sterility is the high risk attribute, any proposed changes in (b) (4) manufacturing process or microbiological testing-related product specification may need to be carefully evaluated.
Endotoxin Pyrogen	Formulation Container Closure Process Parameters Scale/equipment/ Site	Medium	The proposed endotoxin limit (USP <85>) is adequate.	Acceptable	
Assay (API), Stability	Formulation Container Closure Raw Materials Process Parameters Scale/Equipment/ Site	Low	Stability of the API and the drug product, and suitability of commercial container closure system have been well demonstrated. Manufacturing process is well- controlled.	Acceptable	
Assay (anti-oxidant)	Formulation Raw materials Process parameters Scale/equipment/ site	Low	Stability of the API and the drug product, and suitability of commercial container closure system have been well demonstrated. Manufacturing process is well- controlled.	Acceptable	

Uniformity of Dose – Fill/deliverable Volume	Formulation Container Closure Process Parameters Scale/equipment/ site	Low	End product extractable volume testing	Acceptable	
Osmolality	Formulation Raw materials Process parameters Scale/equipment/ site	Low	Osmolality is monitored per USP <785>	Acceptable	
pH	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	Low	The pH is monitored per USP <791>	Acceptable	
Particulate Matter	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	Medium	Particulate matter is monitored per USP <788>.	Acceptable	
Leachable Extractables	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	Low	The extractables and leachables studies indicate no product quality risk from container closure system.	Acceptable	Confirm leachables/extractables profile for any change to processing equipment, processing conditions, container closure system, or storage condition
Appearance	Formulation Raw materials Process Parameters Scale/equipment/ site	Low	The product appearance is routinely monitored.	Acceptable	

Valerie Amspacher

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Valerie Amspacher

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Date: 5/02/2019 02:46:45PM
GUID: 5714dbd10078d2d3d9b60a0ceb819fc3

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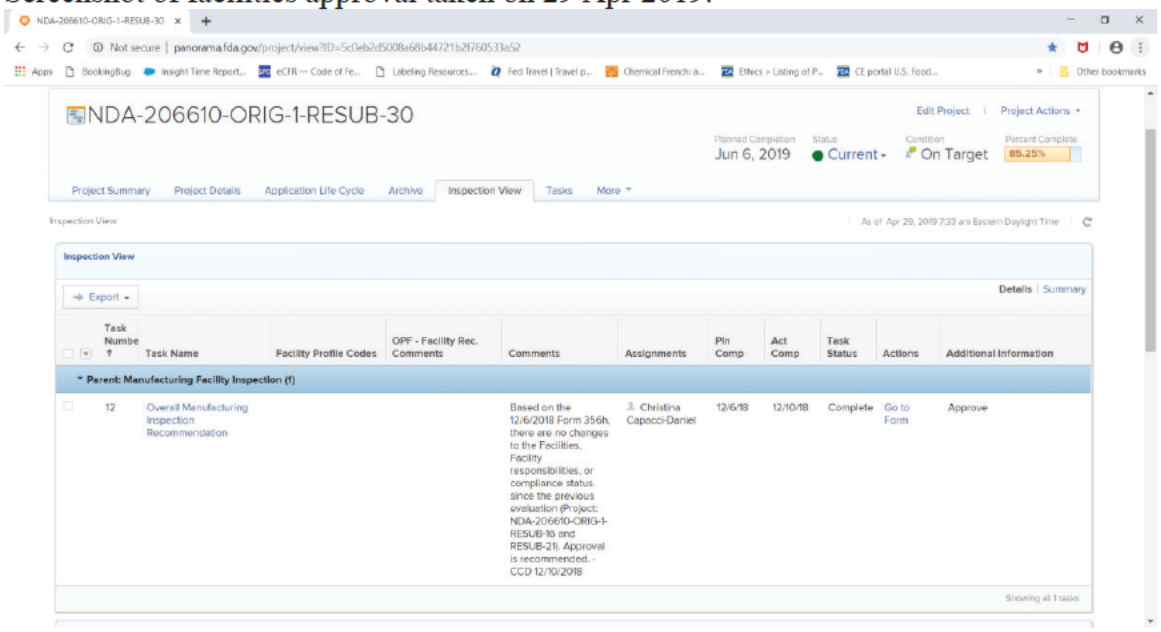
C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

See attachement

Screenshot of facilities approval taken on 29 Apr 2019.



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Julia Pinto

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GUID: 5050dbcb00001294a888a4bdc20a3a58

Chemistry Review Data Sheet

1. NDA 206,610

2. REVIEW #5

3. REVIEW DATE: 11/7/2017

4. REVIEWER: Ciby J. Abraham, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA-206610	08-04-2016

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA-206610	06-07-2017

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan
Address:	781 Chestnut Ridge Road Morgantown, WV 26505
Representative:	Anil Sachdeva, Senior Director - Regulatory Affairs
Telephone:	681-209-5662

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Acetaminophen for Injection
b) Non-Proprietary Name (USAN): Acetaminophen
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: Analgesic

11. DOSAGE FORM: Lyophilized powder for injection

12. STRENGTH/POTENCY: 1g/vial

13. ROUTE OF ADMINISTRATION: Intravenous Infusion

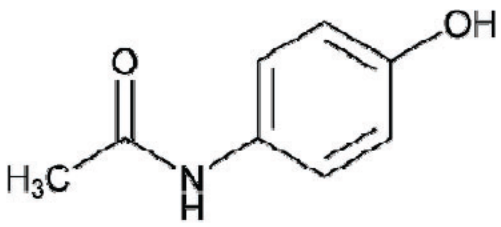
14. Rx/OTC DISPENSED: __X_Rx ___OTC

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:

Acetaminophen

Compendial Name:	Acetaminophen USP
Structural Formula:	
Molecular Formula:	$C_8H_9NO_2$
Molecular Weight:	151.16

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	11/17/2014	
	III			1	Adequate	11/22/2014	
	III			1	Adequate	11/22/14	
	III			1	Adequate	11/22/2014	

[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)
[3] Include reference to location in most recent CMC review

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	22450	Cadence Pharmaceuticals Inc.	Listed drug product that is the basis for submission.

18. CONSULTS/CMC-RELATED REVIEWS: N/A

Chemistry Review Data Sheet

CONSULTS	DATE	STATUS	REVIEWER/COMMENTS

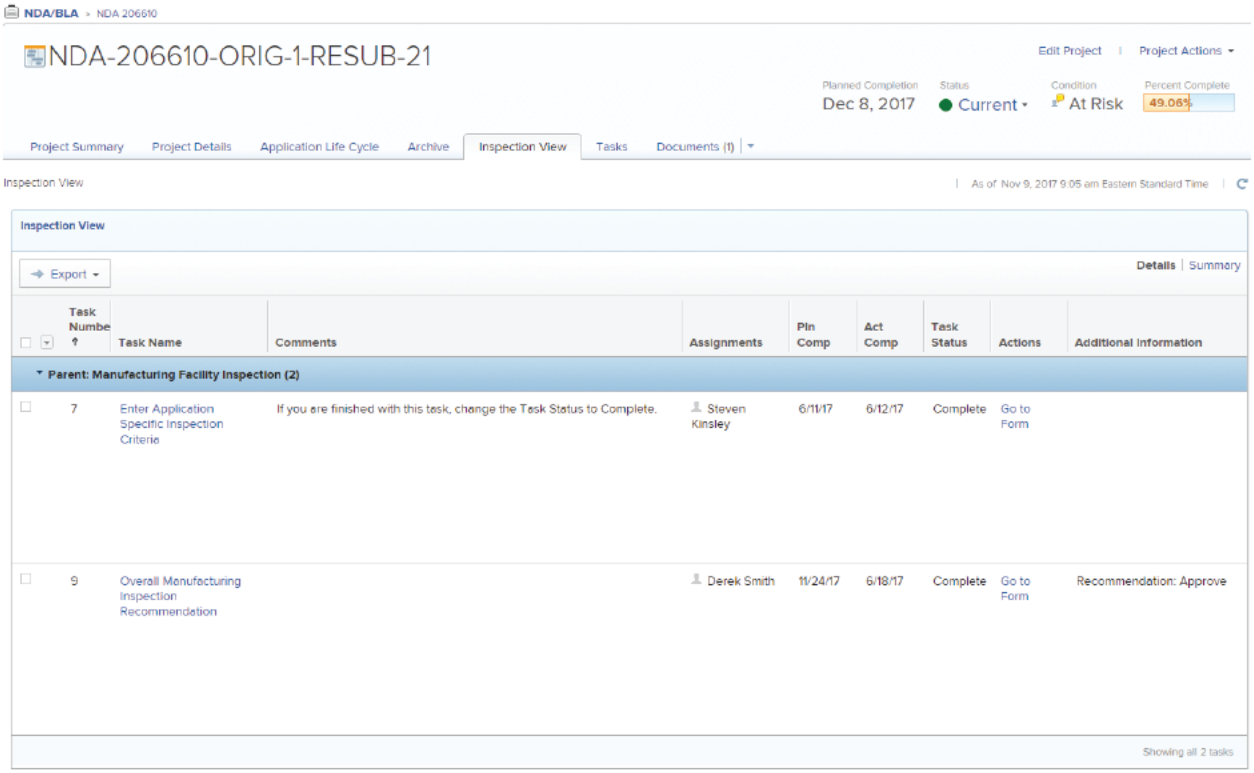
The Executive Summary

I. Introduction

The resubmission response from June 6, 2017 is to a complete response from the Pharmacology/Toxicology group. The purpose of this review is to update the facilities recommendation for this application. Facilities have given an overall recommendation of approval. CMC recommends approval of this submission.

Appendix One.

Screen shot of Inspection View (November 9, 2017 9:05 am) for NDA-206610-ORIG-1-RESUB-21 recommending Approve.



NDA/BLA » NDA 206610

NDA-206610-ORIG-1-RESUB-21

Edit Project | Project Actions

Planned Completion: Dec 8, 2017 | Status: Current | Condition: At Risk | Percent Complete: 49.06%

Project Summary | Project Details | Application Life Cycle | Archive | Inspection View | Tasks | Documents (1)

Inspection View

As of Nov 9, 2017 9:05 am Eastern Standard Time

Inspection View

Export

Details | Summary

Task Number	Task Name	Comments	Assignments	Pln Comp	Act Comp	Task Status	Actions	Additional Information
Parent: Manufacturing Facility Inspection (2)								
7	Enter Application Specific Inspection Criteria	If you are finished with this task, change the Task Status to Complete.	Steven Kinsley	6/11/17	6/12/17	Complete	Go to Form	
9	Overall Manufacturing Inspection Recommendation		Derek Smith	11/24/17	6/18/17	Complete	Go to Form	Recommendation: Approve

Showing all 2 tasks

Ciby
Abraham

Digitally signed by Ciby Abraham
Date: 11/16/2017 01:09:58PM
GUID: 512518c000026e22966a3bf7c15f7809

Chemistry Review Data Sheet

1. NDA 206,610

2. REVIEW #4

3. REVIEW DATE: 1/26/2017

4. REVIEWER: Ciby J. Abraham, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA-206610	05-05-2014

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA-206610	08-04-2016

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan
Address:	781 Chestnut Ridge Road Morgantown, WV 26505
Representative:	Anil Sachdeva, Senior Director - Regulatory Affairs
Telephone:	681-209-5662

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Acetaminophen for Injection
b) Non-Proprietary Name (USAN): Acetaminophen
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: Analgesic

11. DOSAGE FORM: Lyophilized powder for injection

12. STRENGTH/POTENCY: 1g/vial

13. ROUTE OF ADMINISTRATION: Intravenous Infusion

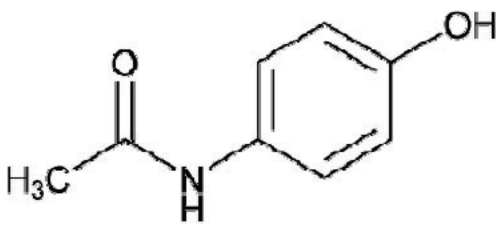
14. Rx/OTC DISPENSED: __X_Rx ___OTC

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:

Acetaminophen

Compendial Name:	Acetaminophen USP
Structural Formula:	
Molecular Formula:	$C_8H_9NO_2$
Molecular Weight:	151.16

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	11/17/2014	
	III			1	Adequate	11/22/2014	
	III			1	Adequate	11/22/14	
	III			1	Adequate	11/22/2014	

[1] Action codes for DMF Table:
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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)
[3] Include reference to location in most recent CMC review

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	22450	Cadence Pharmaceuticals Inc.	Listed drug product that is the basis for submission.

18. CONSULTS/CMC-RELATED REVIEWS: N/A

CONSULTS	DATE	STATUS	REVIEWER/COMMENTS

The Executive Summary

I. Introduction

The Complete Response letter from the second cycle review dated March 10, 2016, the following nonclinical deficiency was communicated to the Applicant:

NONCLINICAL

You have not provided an adequate assessment of the presence of possible extractables from the (b) (4) in the final drug product formulation. Based on your extraction study, as much as approximately (b) (4) mcg/day) of unknown material could be present (b) (4). This exceeds the threshold of toxicological concern of (b) (4) mcg/day and, therefore, requires adequate safety justification based on a toxicological risk assessment for the identified materials.

To address this deficiency, provide the following information:

1. Finalize and submit the study report for the ongoing scientific study designed to analyze the final drug product for the presence of potential leachables from (b) (4)

2. Definitively identify the unknown extractables (b) (4) and determine if they are present in the final drug product formulation.

3. Quantitate and characterize any unidentified foreign material from the (b) (4) that is present in the final drug product. The study must be conducted on the final drug product at release.

4. Submit a revised toxicological risk assessment for every leachable that is above the Toxicological Threshold of Concern of (b) (4) mcg/day. We remind you that GRAS designations are not applicable to intravenous drug products.

5. Include copies of all relevant literature cited as part of your toxicological justification. Any publication that is not in English must be translated.

CMC evaluated the analytical methods for the extractables/leachables report to determine whether the LOD and LOQ are acceptable for the compounds identified in the resubmission. The determination of whether the numerical values are of toxicological concern will be conducted by Dr. Carlic Huynh from the Pharmacology/Toxicology group.

II. Recommendations

A. Recommendation and Conclusion on Approvability

CMC recommends approval of Acetaminophen for Injection. The facilities for all sites in this submission are acceptable.

Leachables Study

CMC reviewed the analytical methods for the leachables study for (b) (4) Acetaminophen for Injection. (b) (4) samples were analyzed by the applicant. Several compounds were identified. In order to quantitate the compounds, the applicant used reference standards for (b) (4) In addition, the applicant also analyzed the samples for (b) (4) matched the reference standards. (b) (4)

TABLE 6
Summary of the LC/UV/MS analysis of the (b) (4) Samples

Retention Time (min)	Compound *	Detection Mode	Related Figure	ID Level	Notes
(b) (4)					

End of Sponsor Material.

Conclusion:

The applicant provided their analytical methodology to determine the extractables/leachables in their (b) (4) As shown above, the LOD and LOQ are established for some of the compounds. The sponsor claims that the unknowns that were detected in the (b) (4) samples exhibited similar UV spectral profile (b) (4) to those already present in the (b) (4) sample indicating that these unknowns may be related to Acetaminophen and/or the product formulation.

The current analytical methods appear to be acceptable. If lower limits of detection and quantitation are needed to fulfill the Pharmacology/Toxicology group's concerns of the extracbles/leachables, a change in the method or analytical technology may be warranted. The applicant provided a toxicological risk assessment for the known and unknown compounds. We defer to the Pharmacology/Toxicology group for the analysis.

APPEARS THIS WAY ON ORIGINAL

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

Julia Pinto

Digitally signed by Julia Pinto
Date: 2/01/2017 09:23:17AM
GUID: 5050dbcb00001294a888a4bdc20a3a58

Ciby Abraham

Digitally signed by Ciby Abraham
Date: 2/01/2017 09:35:53AM
GUID: 512518c000026e22966a3bf7c15f7809

Chemistry Review Data Sheet

1. NDA 206,610

2. REVIEW #3

3. REVIEW DATE: 3/4/2016

4. REVIEWER: Ciby J. Abraham, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA-206610	05-05-2014

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA-206610	09-10-2015

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan
Address:	781 Chestnut Ridge Road Morgantown, WV 26505
Representative:	Anil Sachdeva, Senior Director - Regulatory Affairs
Telephone:	681-209-5662

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Acetaminophen for Injection
b) Non-Proprietary Name (USAN): Acetaminophen
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: Analgesic

11. DOSAGE FORM: Lyophilized powder for injection

12. STRENGTH/POTENCY: 1g/vial

13. ROUTE OF ADMINISTRATION: Intravenous Infusion

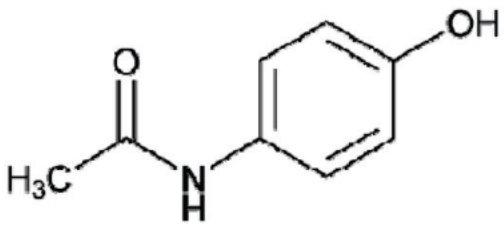
14. Rx/OTC DISPENSED: __X_Rx ___OTC

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:

Acetaminophen

Compendial Name:	Acetaminophen USP
Structural Formula:	
Molecular Formula:	$C_8H_9NO_2$
Molecular Weight:	151.16

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	11/17/2014	
	III			1	Adequate	11/22/2014	
	III			1	Adequate	11/22/14	
	III			1	Adequate	11/22/2014	

[1] Action codes for DMF Table:
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2 –Type 1 DMF
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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)
[3] Include reference to location in most recent CMC review

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	22450	Cadence Pharmaceuticals Inc.	Listed drug product that is the basis for submission.

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	DATE	STATUS	REVIEWER/COMMENTS
Facilities	3/4/2016	Withhold	

The Executive Summary

I. Introduction

The original submission of this NDA was recommended, by CMC, as a complete response, because of the extractables [redacted]. The extractable/leachable study demonstrated that a maximum of [redacted] ug of unidentified material may be present in [redacted] of lyophilized acetaminophen drug product. Therefore, the first cycle deficiency was combined with those of the Pharmacology/Toxicology group and listed in the complete response letter from February 2015, as follows:

You have not provided an adequate characterization of potential leachables from the [redacted]. Based on your extraction study, as much as approximately [redacted] mcg/day) of unknown material could be present [redacted] This exceeds the threshold of toxicological concern of [redacted] mcg/day and, therefore, requires adequate safety justification based on a toxicological risk assessment for the identified materials.

To address this deficiency, identify the extractables from [redacted] extraction study and determine if they are present in the drug product formulation. Quantitate and characterize any unidentified foreign material from [redacted] that is present in the drug product. Submit an adequate toxicological risk assessment for any leachable that is above the Toxicological Threshold of Concern of [redacted] mcg/day.

In this resubmission, the Applicant has provided a toxicology assessment for all possible impurities, but has not adequately responded to the request to conduct the extraction study, on the final drug product.

II. Recommendations

A. Recommendation and Conclusion on Approvability

The Applicant has not adequately responded to the CMC CR of February 2015. The sponsor provides a [redacted] /extractable study that shows a maximum of [redacted] ug of unidentified material that may be present in the lyophilized acetaminophen. However, they did not quantitate and characterize any unidentified material from the [redacted] that is present in the actual drug product as stated in the February complete response letter to the firm. Therefore, in order to resolve the complete response, the sponsor will need to provide the full characterization of the unidentified material that is present in their product from their [redacted] process. The study must be conducted on the product itself at release. Evaluation of the

compound(s) and specifications will be evaluated by CMC and the pharmacology/toxicology group. The Office of Compliance has given an overall recommendation of withhold for the drug product manufacturing site Agila Specialties Private Limited (FEI: 3007648351) and for Agila Specialties Private Limited Control Testing Laboratory (FEI: 3003813519).

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 drug substance, Acetaminophen (APAP), USP, is manufactured by (b) (4) APAP is a white crystalline powder with an approximate solubility of (b) (4) (b) (4) Acetaminophen is packaged in (b) (4) Acetaminophen has a (b) (4) month retest period when stored at excursion permitted to (b) (4).

The drug product Acetaminophen for Injection is manufactured by Agila Specialties Private Limited. The product is a sterile white to off white lyophilized powder or cake. (b) (4) contains no antimicrobial preservatives. The white to off white lyophilized powder or cake is filled in 100 mL/28 mm, USP & Ph.Eur. (b) (4) glass vial with 28 mm grey (b) (4) stopper and 28 mm flip off aluminum red seal. The lyophilized powder is reconstituted by adding 98 mL of water for injection and shaking it (b) (4) fully dissolve. The shelf life of the lyophilized powder is 24 months at 20 C to 25°C (68°F to77°F). The solution is stable for 12 hours at 20°C to 25°C.

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

Acetaminophen for injection 1 g/vial is a generic medicinal product containing the active ingredient acetaminophen. Acetaminophen is a non-salicylate antipyretic and non-opioid analgesic agent used in management of mild to moderate pain, moderate to severe pain with adjunctive opioid analgesics and fever.

C. Basis for Approvability or Not-Approval Recommendation

There is insufficient information submitted to the chemistry, manufacturing and controls to assess the safety of the drug product. Specifically, the sponsor has not provided adequate information to assess the unidentified impurity found in the (b) (4) of the drug product during manufacture. Therefore, this application is recommended as a complete response pending resolution of the CMC deficiency and the deficiencies from the facility inspection of the drug product manufacturing site Agila Specialties Private Limited (FEI: 3007648351) and the Agila Specialties Private Limited Control Testing Laboratory (FEI: 3003813519), sited by the Office of Compliance.

CMC Deficiency:

1. Based on (b) (4) /extractable study, a maximum of (b) (4) ug of unidentified material may be present in (b) (4) the lyophilized acetaminophen drug product. The Sponsor has not identified and quantitated the extractables in the drug product at release.

Resolving CMC Deficiency:

1. Quantitate and characterize any unidentified extractable from (b) (4) that is present in the drug product. The study must be conducted on the final drug product at release.

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

CHEMISTRY REVIEW

NDA 206610

Acetaminophen for Injection

1g/vial

Agila Specialties Private Limited

Ciby J. Abraham, Ph.D.

ONDP/DIV II/Branch IV
for
Division of Anesthesia, Analgesia & Addiction Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 206,610

2. REVIEW #1

3. REVIEW DATE: 2/3/2015

4. REVIEWER: Ciby J. Abraham, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA-22450	05-13-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA- (b) (4)	05-03-2014
MF- (b) (4)	03-06-2004
Quality Amendment	01-15-2015
Quality Amendment	01-21-2015

7. NAME & ADDRESS OF APPLICANT:

Name:	Agila Specialties Private Limited
Address:	Strides House, Opp. to IIM-B, Bilekahalli, Bannerghatta Road, Banglore, India 560076
Representative:	Anil Sachdeva, Senior Director - Regulatory Affairs
Telephone:	681-209-5662

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Acetaminophen for Injection
b) Non-Proprietary Name (USAN): Acetaminophen
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: N/A
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Analgesic

11. DOSAGE FORM: Lyophilized powder for injection

12. STRENGTH/POTENCY: 1g/vial

13. ROUTE OF ADMINISTRATION: Intravenous Infusion

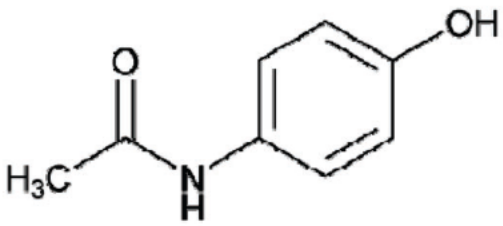
14. Rx/OTC DISPENSED: __X_Rx ___OTC

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:

Acetaminophen

Compendial Name:	Acetaminophen USP
Structural Formula:	
Molecular Formula:	$C_8H_9NO_2$
Molecular Weight:	151.16

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	11/17/2014	
	III			1	Adequate	11/22/2014	
	III			1	Adequate	11/22/14	
	III			1	Adequate	11/22/2014	

[1] Action codes for DMF Table:
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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)
[3] Include reference to location in most recent CMC review

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	22450	Cadence Pharmaceuticals Inc.	Listed drug product that is the basis for submission.

Chemistry Review Data Sheet

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	DATE	STATUS	REVIEWER/COMMENTS
EES		Pending	Juandria Williams
Biopharm	8/27/2014	Acceptable	Kelly Kitchens
Microbiology		Pending	Vinayak Pawar

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

We recommend a complete response from a Chemistry, Manufacturing, and Control (CMC) perspective for the following reasons. The sponsor provides a [(b) (4)]/extractable study that shows a maximum of [(b) (4)] ug of unidentified material that may be present in [(b) (4)] lyophilized acetaminophen. CMC sent out an information request on 11/25/2014 and had two teleconferences on 12/5/2014 and 1/22/2015 with the sponsor addressing this issue. The sponsor stated they will characterize the unidentified material but has not provided any information to date. Therefore, in order to resolve the complete response, the sponsor will need to provide the full characterization of the unidentified material that is present in their product from their [(b) (4)] process. Evaluation of the compound(s) and specifications will be evaluated by CMC and the pharmacology/toxicology group. An adequate CMC recommendation is further pending the overall recommendation from the Office of Compliance and the microbiology group.

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 drug substance, Acetaminophen (APAP), USP, is manufactured by [(b) (4)] APAP is a white crystalline powder with an approximate solubility of [(b) (4)] [(b) (4)] Acetaminophen is packaged in [(b) (4)] Acetaminophen has a [(b) (4)] month retest period when stored at [(b) (4)], excursion permitted to [(b) (4)]

The drug product Acetaminophen for Injection is manufactured by Agila Specialties Private Limited. The product is a sterile white to off white lyophilized powder or cake. [(b) (4)] contains no antimicrobial preservatives. The white to off white lyophilized powder or cake is filled in 100 mL/28 mm, USP & Ph.Eur. [(b) (4)] glass vial with 28 mm grey [(b) (4)] stopper and 28 mm flip off aluminum red seal. The lyophilized powder is reconstituted by adding 98 mL of water for injection [(b) (4)] to fully dissolve. The shelf life of the

lyophilized powder is 24 months at 20°C to 25°C (68°F to77°F). The solution is stable for 12 hours at 20°C to 25°C.

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

Acetaminophen for injection 1 g/vial is a generic medicinal product containing the active ingredient acetaminophen. Acetaminophen is a non-salicylate antipyretic and non-opioid analgesic agent used in management of mild to moderate pain, moderate to severe pain with adjunctive opioid analgesics and fever.

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has not provided adequate information in the manufacturing and controls for the drug product. The application is currently recommended as a complete response until the sponsor provides sufficient evidence of the quantity and characterization of the unidentified foreign material from (b) (4) into the drug product. (b) (4) The overall recommendation for the site is withhold.

CMC Deficiency:

1. Based on (b) (4) extractable study, a maximum of (b) (4) ug of unidentified material may be present in (b) (4) the lyophilized acetaminophen drug product.

Resolving CMC Deficiency:

1. Quantitate and characterize any unidentified foreign material from (b) (4) that is present in the drug product.

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****
Sterility	Formulation Container closure Process parameters Scale/Equipment	H			Please see the review from the microbiologist, Vinayak Pawar.
Endotoxin	Formulation Container	M			Please see the review from the

	closure Process parameters Scale/Equipment				microbiologist, Vinayak Pawar.
Assay Stability	Formulation Container closure Process parameters Scale/Equipment	L	-	-	-
Physical stability (Lyophilized small molecule)	Formulation Container closure Process parameters Scale/Equipment	L	-	-	-
Uniformity of dose (Deliverable volume)	Process parameter Equipment	L	-	-	-
Osmolality	Formulation Container closure Process parameters Scale/Equipment	L	-	-	-
pH	Formulation Container closure Process parameters Scale/Equipment	L	-	-	-
Particulate matter	Formulation Container closure Process parameters Scale/Equipment	M	(b) (4)	Acceptable	(b) (4)
Leachable/extractable	Formulation Container closure Process parameters Scale/Equipment	L	-	-	
Reconstitution time	Formulation Container closure Process parameters Scale/Equipment	M	(b) (4)	Acceptable	According to the sponsor, it takes NMT (b) (4) minutes to reconstitute 1 gram of lyophilized product to dissolve in 98 mL of water.
Moisture content (lyophilized)	Formulation Container closure Process parameters Scale/Equipment	L	-	-	
Appearance (caking)	Formulation Container closure Process parameters Scale/Equipment	M	No risk mitigation approach	Acceptable	The lyophilized product does have caking in the vial. This does not impact the quality of the

					drug product because 98 mL of water is placed into the vial and shaken until it is fully dissolved (NMT (b) (4) min).
Appearance (turbidity)	Formulation Container closure Process parameters Scale/Equipment	L	-	-	

*Risk ranking applies to product attribute/CQA
**For example, post marketing commitment, knowledge management post approval, etc.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Ciby J. Abraham, Ph.D., CMC Reviewer
Julia C. Pinto, Ph.D., Acting Branch Chief

C. CC Block

Biopharmaceutics Reviewer	KITCHENS, KELLY M.	CDER/ONDQA	05/14/2014
Clinical Pharmacology Reviewer	NALLANI, SRIKANTH C.	CDER/OCP/DCPII	05/14/2014
Non-Clinical Reviewer	HUYNH, CARLIC K.	CDER/ODEII/DAAAP	05/07/2014
OSE Regulatory Project Manager	SKARUPA, LISA M.	CDER/OSEIO/OSEIO PMS	05/15/2014
Product Quality Reviewer	ABRAHAM, CIBY J.	CDER/ONDQA/DNDQAIII/DNDQAIII BVIII	05/14/2014
Product Quality Regulatory Project Manager	RIVERA, LUZ E.	CDER/ONDQA	09/22/2014
Regulatory Project Manager	HILFIGER, CHRISTOPHER M.	CDER/ODEII/DAAAP	05/07/2014

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Post-Approval Commitments (For NDA only)

Reviewer's Assessment: N/A

Lifecycle Management Considerations

N/A

LABELING

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Yes
Dosage form, route of administration	Yes
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Yes

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Yes

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Yes
Strengths: in metric system	Yes
Active moiety expression of strength with equivalence statement (if applicable)	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Yes

4. ***Section 11 Description***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Yes
Dosage form and route of administration	Yes
Active moiety expression of strength with equivalence statement (if applicable)	N/A
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Yes
Statement of being sterile (if applicable)	Yes
Pharmacological/ therapeutic class	Yes
Chemical name, structural formula, molecular weight	Yes
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	pH not listed, will discuss with team to see if pH needed, if it is, will send an IR to have it included

5. ***Section 16 How Supplied/Storage and Handling***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Yes
Available units (e.g., bottles of 100 tablets)	Yes
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes
Special handling (e.g., protect from light)	Yes
Storage conditions	Yes
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Yes

Reviewer's Assessment of Package Insert: Adequate.
The Prescribing Information complies with all regulatory requirements from a CMC perspective.

II. Labels:

1. ***Container Label***

2. ***Carton Label***

(b) (4)

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Yes	Yes
Dosage strength	Yes	Yes
Net contents	Yes	Yes
"Rx only" displayed prominently on the main panel	Yes	Yes
NDC number (21 CFR 207.35(b)(3)(i))	Yes	Yes
Lot number and expiration date (21 CFR 201.17)	Yes	Yes
Storage conditions	Yes	Yes
Bar code (21CFR 201.25)	Yes	Yes
Name of manufacturer/distributor	Yes	Yes
And others, if space is available	N/A	N/A

Reviewer's Assessment of Labels: Adequate.
The labels comply with all regulatory requirements from a CMC perspective.

Valerie Amspacher

Digitally signed by Valerie Amspacher
Date: 4/29/2019 07:40:29AM
GUID: 5714dbd10078d2d3d9b60a0ceb819fc3

Julia Pinto

Digitally signed by Julia Pinto
Date: 4/29/2019 11:09:11AM
GUID: 5050dbcb00001294a888a4bdc20a3a58

MICROBIOLOGY

Product Background: The drug product is a [redacted] (b) (4) filled, lyophilized powder indicated for the treatment moderate pain and fever reduction.

NDA: 206610 (CR Response)

Drug Product Name / Strength: Acetaminophen / 1 g/vial

Route of Administration: IV

Applicant Name: Mylan Laboratories Limited

Manufacturing Site:
Mylan Laboratories Limited (Specialty Formulation Facility)
19-A, Plot No. 284-B/1
Bommasandra Jigani Link Road
Industrial Area, Anekal Taluk
Bangalore, Karnataka, India 560105

Method of Sterilization: [redacted] (b) (4)

Review Recommendation: Adequate

Review Summary: Drug product is [redacted] (b) (4) and lyophilized. This review covers the validation of [redacted] (b) (4) and sterilization of related components.

List Submissions Being Reviewed:
05/05/2014
12/06/2018

Highlight Key Outstanding Issues from Last Cycle: See "Remarks" below.

Remarks: The original submission for this application was received 05/05/2014 and was reviewed and found adequate for Microbiology on 02/18/2015. However, the applicant was issued a Complete Response letter by the Agency dated 02/27/2015. A second Complete Response letter was issued 12/06/2017. The subject submission contains [redacted] (b) (4) validation information for equipment which has been installed/upgraded since the original Microbiology review was performed (See "Note to Reviewer" below).

Concise Description Outstanding Issues Remaining: NA

Supporting Documents: N206610R1.doc, dated 18 February 2015, reviewed the original NDA submission with a recommendation of "Adequate."

List Number of Comparability Protocols (ANDA only): N/A

Note to Reviewer – The original submission was reviewed and found adequate in N206610R1.doc, dated 18 February 2015. Drug product is manufactured in (b) (4) of the proposed manufacturing facility. The applicant states that there have been no changes to the overall manufacturing process, but (b) (4) has been refurbished since the original submission, with several new pieces of equipment installed and upgrades performed to some existing equipment. No changes are reported for manufacturing equipment used in (b) (4) Additionally, no changes are reported for the drug product formulation, batch size, container-closure system, release/stability specifications, analytical methods or labeling. (b) (4) This review will cover only those sections for which changes have been reported.

P. 3.5 Process Validation and/or Evaluation

(b) (4) ***Manufacturing Process***

(b) (4)

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Jason God

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Date: 1/18/2019 10:22:04AM
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Denise Miller

Digitally signed by Denise Miller
Date: 1/18/2019 10:42:17AM
GUID: 508da7280002a5d546459b998253d1aa

Product Quality Microbiology Review

February 18, 2015

NDA: 206610

Drug Product Name
Proprietary: Acetaminophen Injection
Non-proprietary: Acetaminophen Injection 1g/vial

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
May 02, 2014	May 05, 2014	May 14, 2014	May 16, 2014

Submission History (for 2nd Reviews or higher) – N/A

Applicant/Sponsor Name: Agila (Formerly Strides) Specialties Private Ltd.
Address: 201 South Main Street, Suite 3, Lambertville NJ 08530, Tel: (609) 773-5000
Representative: Anil Sachdeva, Sr. Director, Regulatory Affairs TEL: (410)-603-1380

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: Recommend Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original Drug Application

2. SUBMISSION PROVIDES FOR: New Drug Application

3. MANUFACTURING SITE: Agila Specialties Private Ltd., Bangalore, India 560105.

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Lyophilized drug product 1g/vial for intravenous administration.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Managing moderate pain and fever reduction.

B. SUPPORTING/RELATED DOCUMENTS: None.

C. REMARKS: Agila Specialties Private Limited herewith submitting a New Drug Application (NDA 206610) for Acetaminophen for Injection [1 g/vial]. This is an electronic submission.

filename: **N206610R1**

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommend Approval.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product is manufactured by [redacted] (b) (4) and lyophilization.

B. Brief Description of Microbiology Deficiencies – None.

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

D. Contains Potential Precedent Decision(s) - ☐ **Yes** ☒ **No**

III. Administrative

A. Reviewer's Signature _____
Vinayak B. Pawar, Ph.D., Sr. Review Microbiologist, OPQ/CDER

B. Endorsement Block _____
Stephen E. Langille, Ph.D., Acting Chief Branch III, OPQ/CDER

C. CC Block
N/A

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Chemistry Review Data Sheet

1. NDA 206,610

2. REVIEW #2

3. REVIEW DATE: 2/26/2015

4. REVIEWER: Ciby J. Abraham, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA-22450	05-13-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA-(b) (4)	05-03-2014
MF-(b) (4)	03-06-2004
Quality Amendment	01-15-2015
Quality Amendment	01-21-2015

7. NAME & ADDRESS OF APPLICANT:

Name:	Agila Specialties Private Limited
Address:	Strides House, Opp. to IIM-B, Bilekahalli, Bannerghatta Road, Banglore, India 560076
Representative:	Anil Sachdeva, Senior Director - Regulatory Affairs
Telephone:	681-209-5662

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Acetaminophen for Injection
b) Non-Proprietary Name (USAN): Acetaminophen
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: Analgesic

11. DOSAGE FORM: Lyophilized powder for injection

12. STRENGTH/POTENCY: 1g/vial

13. ROUTE OF ADMINISTRATION: Intravenous Infusion

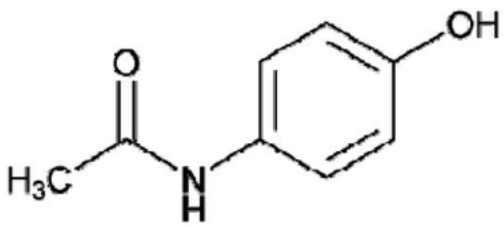
14. Rx/OTC DISPENSED: __X_Rx ___OTC

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:

Acetaminophen

Compendial Name:	Acetaminophen USP
Structural Formula:	
Molecular Formula:	$C_8H_9NO_2$
Molecular Weight:	151.16

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	11/17/2014	
	III			1	Adequate	11/22/2014	
	III			1	Adequate	11/22/14	
	III			1	Adequate	11/22/2014	

[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)
[3] Include reference to location in most recent CMC review

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	22450	Cadence Pharmaceuticals Inc.	Listed drug product that is the basis for submission.

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	DATE	STATUS	REVIEWER/COMMENTS
EES	2/20/2015	Withhold	Juandria Williams
Biopharm	8/27/2014	Acceptable	Kelly Kitchens
Microbiology	2/17/2015	Acceptable	Vinayak Pawar

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

We recommend a complete response from a Chemistry, Manufacturing, and Control (CMC) perspective for the following reasons. The sponsor provides a (b) (4) /extractable study that shows a maximum of (b) (4) ug of unidentified material that may be present in (b) (4) lyophilized acetaminophen. CMC sent out an information request on 11/25/2014 and had two teleconferences on 12/5/2014 and 1/22/2015 with the sponsor addressing this issue. The sponsor stated they will characterize the unidentified material but has not provided any information to date. Therefore, in order to resolve the complete response, the sponsor will need to provide the full characterization of the unidentified material that is present in their product from their (b) (4) process. Evaluation of the compound(s) and specifications will be evaluated by CMC and the pharmacology/toxicology group. The Office of Compliance has given an overall recommendation of withhold for the drug product manufacturing site Agila Specialties Private Limited (FEI: 3007648351) and for Agila Specialties Private Limited Control Testing Laboratory (FEI: 3003813519). The microbiology group has given an overall recommendation of 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 drug substance, Acetaminophen (APAP), USP, is manufactured by (b) (4) APAP is a white crystalline powder with an approximate solubility of (b) (4). Acetaminophen is packaged in (b) (4). Acetaminophen has a (b) (4) month retest period when stored at (b) (4), excursion permitted to (b) (4)

The drug product Acetaminophen for Injection is manufactured by Agila Specialties Private Limited. The product is a sterile white to off white lyophilized powder or cake. (b) (4) and contains no antimicrobial

preservatives. The white to off white lyophilized powder or cake is filled in 100 mL/28 mm, USP & Ph.Eur. [redacted] glass vial with 28 mm grey [redacted] stopper and 28 mm flip off aluminum red seal. The lyophilized powder is reconstituted by adding 98 mL of water for injection [redacted] The shelf life of the lyophilized powder is 24 months at 20 C to 25 C (68 F to77°F). The solution is stable for 12 hours at 20°C to 25°C.

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

Acetaminophen for injection 1 g/vial is a generic medicinal product containing the active ingredient acetaminophen. Acetaminophen is a non-salicylate antipyretic and non-opioid analgesic agent used in management of mild to moderate pain, moderate to severe pain with adjunctive opioid analgesics and fever.

C. Basis for Approvability or Not-Approval Recommendation

There is insufficient information submitted to the chemistry, manufacturing and controls to assess the safety of the drug product. Specifically, the sponsor has not provided adequate information to assess the unidentified impurity found in the [redacted] of the drug product during manufacture. Therefore, this application is recommended as a complete response pending resolution of the CMC deficiency and the deficiencies from the facility inspection of the drug product manufacturing site Agila Specialties Private Limited (FEI: 3007648351) and the Agila Specialties Private Limited Control Testing Laboratory (FEI: 3003813519), sited by the Office of Compliance.

CMC Deficiency:

1. Based on [redacted] extractable study, a maximum of [redacted] ug of unidentified material may be present in [redacted] the lyophilized acetaminophen drug product.

Resolving CMC Deficiency:

1. Quantitate and characterize any unidentified foreign material from [redacted] that is present in the drug product.

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

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 206610	**Reviewer:** Kelly M. Kitchens, Ph.D.	
Submission Date:	May 2, 2014		
Division:	Division of Anesthesia, Analgesia, and Addiction Products	**Team Lead:** Tapash Ghosh, Ph.D.	
Applicant:	Agila Specialties Private Limited	**Acting Supervisor:** Paul Seo, Ph.D.	
Trade Name:	N/A	**Date Assigned:**	May 14, 2014
Established Name:	Acetaminophen for Injection	**Date of Review:**	August 25, 2014
Indication:	The management of mild to moderate pain, the management of moderate to severe pain with adjunctive opioid analgesics and reduction of fever.	**Type of Submission:** New Drug Application 505(b)(2)	
Formulation/ strengths	1 g/vial		
Route of Administration	Intravenous infusion		
Type of Review:	Biowaiver Request		

SUMMARY:

Background: The proposed drug product, Acetaminophen for Injection, is a sterile lyophilized powder or cake containing 1 g acetaminophen per vial (100 mL glass vial), and is indicated for:

- the management of mild to moderate pain;
- the management of moderate to severe pain with adjunctive opioid analgesics;
- the reduction of fever.

The reference drug product for Acetaminophen for Injection is Ofirmev® (acetaminophen) for Injection (NDA 22450, approved November 2, 2010), which has the same indication as Acetaminophen for Injection. Ofirmev® (acetaminophen) for Injection is approved for intravenous administration over 15 minutes, with a maximum daily dose of 4000 mg in 24 hours (for patients 13 and older weighing ≥ 50 kg). After reconstitution to with 100 mL sterile water for injection, the contents of the Acetaminophen for Injection vial should be administered intravenously over 15 minutes.

Submission: The Applicant requests a biowaiver for Acetaminophen for Injection (1 g/vial) per 21 CFR § 320.22 (b)(1), based on the following:

- The proposed drug product is a clear, sterile solution after reconstitution and

dilution; it is intended solely for administration by injection (intravenous infusion).

- The proposed drug product claims the same active ingredients in the same concentration as presented on the labeling of the reference drug product, Ofirmev (acetaminophen) for Injection that is the subject of an approved NDA 22450 held by Cadence Pharms, and approved November 2, 2010.

Review: The Biopharmaceutics review is focused on the evaluation and approvability of the information submitted to support the biowaiver request.

RECOMMENDATION:

The waiver for in vivo bioavailability/bioequivalence studies for Acetaminophen for Injection, 1 g/vial, is granted. From the Biopharmaceutics perspective, NDA 206610 for Acetaminophen for Injection, 1 g/vial, is recommended for approval.

Signature	**Signature**
Kelly M. Kitchens, Ph.D.	Tapash Ghosh, Ph.D.
Biopharmaceutics Reviewer	Biopharmaceutics Team Leader
Office of New Drug Quality Assessment	Office of New Drug Quality Assessment

cc. PSeo.

BIOPHARMACEUTICS ASSESSMENT

Drug Product:

- Based on the properties of the drug substance, characterization of the liquid reference drug product, and consideration of the reference drug product labeling and intended patient population, the quality target product profile (QTPP) was defined for Acetaminophen for Injection [1 g/vial] developed by Agila Specialties.

QTPP Elements		Target	Justification
Dosage form		Lyophilized injection	505 (b)(2) approach, change in dosage form
Dosage strength		1 g/vial (10 mg/mL after reconstitution)	Pharmaceutical and therapeutic equivalent requirement - same strength (1000 mg/100 mL) as RLD after reconstitution.
Dose		4g/day	Pharmaceutical and therapeutic equivalent requirement - same dose
Route of administration		IV infusion	Pharmaceutical and therapeutic equivalent requirement - same route of administration as that of RLD
Pharmacokinetics		Similar as RLD	Bioequivalence requirement - Should have similar to RLD after reconstitution
Stability		At least 24-month shelf-life at room temperature	Equivalent to or better than liquid RLD shelf-life
Drug product quality attributes	Description	White to off-white lyophilized powder or cake (b) (4) vial (b) (4) stopper and aluminum seal.	
	Identification by HPLC	By HPLC- The retention time of the major peak in the chromatogram of the standard preparation should correspond to that of the retention time of the main peak in sample preparation, as obtained in the test for assay.	
	Identification by TLC	By TLC – The principal spot in the chromatogram obtained with sample preparation should correspond to that in the chromatogram obtained with the standard preparation.	
	Reconstitution time	NMT (b) (4) minutes	
	Uniformity of dosage units	The acceptance value of 10 dosage units should be less than or equal to L1% [L1 is (b) (4) %]	

QTPP Elements		Target	Justification
	Completeness and clarity of solution	As per USP	
	Water by KF	Not more than (b)(4) %w/w	
	pH	Between 4.5 and 6.5	
	Color value at 430 nm	Not more than (b)(4)	
	Light transmission at 650 nm	Not less than (b)(4) %	
	Osmolality	290 ± (b)(4) mOsmol	
	Sterility	Must be sterile	
	Bacterial endotoxins by LAL test	Not more than (b)(4) EU/mg of Acetaminophen	
	Particulate matter by light obscuration	(b)(4)	
	Assay by HPLC	(b)(4) % to (b)(4) % of label claim	
	Related substances by HPLC (b)(4) Maximum single unknown impurity Total impurities	Not more than (b)(4) Not more than Not more than Not more than Not more than Not more than (b)(4)	
	L-cysteine hydrochloride content	(b)(4) of label claim	
	Mannitol Content	(b)(4) % of label claim	
	(b)(4)	Not more than (b)(4)	
	USP <1>requirement for injection	Should meet the requirement	
Container closure system		100mL USP (b)(4) (b)(4) vials.	Needed to achieve the target shelf-life and to ensure product integrity during shipping
Administration/Concurrence with labeling		Similar as liquid RLD	Generic product requirement - Labeling similarity with additional instruction for reconstitution.
Alternative methods of administration		None	None are listed in the RLD label.

Biowaiver Request:

- The Applicant provided the following comparison of the reference drug product formulation compared to the proposed drug product formulation:

Reference Listed Drug: Ofirmev (Acetaminophen) injection by Cadence Pharms		Proposed Drug Product: Acetaminophen for Injection [1 g/vial] by Agila Specialties	
Ingredients	**Quantity/100 mL**	**Ingredients**	**Quantity/vial**
Acetaminophen, USP	1000.0 mg	Acetaminophen	1000.0 mg
Mannitol, USP	3850.0 mg	Mannitol	3850.0 mg
Cysteine hydrochloride monohydrate, USP	25.0 mg	L-Cysteine hydrochloride monohydrate	25.0 mg
Dibasic sodium phosphate, USP	10.4 mg	Dibasic sodium phosphate (b) (4)	13.0 mg
Hydrochloric acid and /or Sodium hydroxide	Q.S. for pH adjustment	Hydrochloric acid and /or Sodium hydroxide	Q.S. for pH adjustment
		(b) (4)	(b) (4)
		(b) (4)	Q.S. to (b) (4)
		(b) (4)	Q.S.

(b) (4)

- In addition, the Applicant provided a comparative table for the quality attributes of Acetaminophen for Injection per the Agency's preliminary comments (November 2, 2012) to the pre-IND 116240 meeting package:

Sponsor question: *Agila/Strides is intending to request a waiver of in vivo bioavailability requirements pursuant to 21 CFR §320.22. Acetaminophen for Injection is recommended for intravenous administration. Based on the CMC information contained in Attachment 3.1, and that the labeling is identical to that of the RLD (except for changes in the drug product presentation) does the Division concur that the proposed product is eligible for a waiver of in vivo bioavailability requirements pursuant to 21 CFR §320.22 ?*

Agency response: *Your proposal for a biowaiver seems appropriate. Please include the BA/BE waiver request for your product in the NDA and provide a justification with supportive information/data for any differences in the formulations. Also, include a table comparing (side to side) the formulations, osmolarity, pH, indication, and labeling claims for your proposed product vs. the listed product.*

	Reference Listed Drug: Ofirmev (Acetaminophen) injection by Cadence Pharms*	Proposed Drug Product: Acetaminophen for Injection [1 g/vial] by Agila Specialties		
		Exhibit Batch# 7600649	Exhibit Batch# 7600661	Exhibit Batch# 7600666
Osmolality	(b) (4)	(b) (4)		
pH	5.598	5.60	5.62	5.60
Indication	• the management of mild to moderate pain • the management of moderate to severe pain with adjunctive opioid analgesics • the reduction of fever.	• the management of mild to moderate pain • the management of moderate to severe pain with adjunctive opioid analgesics • the reduction of fever.		
Label claims	Each 100 mL contains 1000 mg acetaminophen, USP	Each vial contains 1000 mg acetaminophen, USP [Concentration after reconstitution: 1000 mg/100 mL]		
Route of administration	Intravenous (Infusion)	Intravenous (Infusion)		

**Information based on rld (Ofirmev) package insert.*

Biopharmaceutics Reviewer comments:

- 13.0 mg dibasic sodium phosphate (dihydrate) is equivalent to 10.4 mg dibasic sodium phosphate (anhydrous):

  $$\frac{13.0 \text{ mg dihydrate}}{177.99 \text{ g/mol dihydrate}} \times 141.96 \text{ g/mol anhydrous} = 10.4 \text{ mg anhydrous}$$

  Therefore, the comparative formulation table indicates that the reference drug product formulation and the proposed drug product formulation contain the same active and inactive ingredients in the same concentrations.
- The reference drug product and proposed drug product have similar pH values:
  - Reference product pH = 5.598
  - Proposed product, batch # 7600649, pH = 5.60
  - Proposed product, batch # 7600661, pH = 5.62
  - Proposed product, batch # 7600666, pH = 5.60
- The mean osmolality of the proposed drug product (312 mOsmol/kg) is 13.9% greater than the reported osmolality of the reference drug product (274 mOsmol/kg). Internal discussion with the Division of Anesthesia, Analgesia, and Addiction Products clinical team determined that this difference in osmolality does not pose any safety concerns.
- The proposed drug product meets the following CFR § 320.22 (b)(1) criteria for a biowaiver:
  i. The drug product is a parenteral solution intended solely for administration by injection; and
  ii. The dug product contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.
- The Applicant has provided adequate information to support the biowaiver request. Therefore, the waiver for in vivo bioavailability/bioequivalence studies for Acetaminophen for Injection, 1 g/vial, is granted.

RECOMMENDATION:

The waiver for in vivo bioavailability/bioequivalence studies for Acetaminophen for Injection, 1 g/vial, is granted. From the Biopharmaceutics perspective, NDA 206610 for Acetaminophen for Injection, 1 g/vial, is recommended for approval.

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/s/

KELLY M KITCHENS
08/27/2014

TAPASH K GHOSH
08/27/2014

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/s/

SWATI A PATWARDHAN
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