CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022450Orig1s000

CHEMISTRY REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drug Quality Assessment

Memorandum

Date: November 1, 2010

From: Martin Haber, Ph.D., Review Chemist

Subject: Overall OC Recommendation for NDA 22-450 Acetaminophen Injection

The original NDA submission received a complete response action on 2/10/2010 because of a withhold approval recommendation for the drug product manufacturing facility, Baxter Healthcare Corporation, in Cleveland, MS. The withhold recommendation was made due to significant issues found during an inspection of the Baxter facility in January and February 2010.

Specifically, as described in the Addendum to the Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls by Dr. P. Peri dated 2/10/2010, the investigator found several unusual findings related to particulate matter in the registration stability batch and a form 483 was issued to the Baxter plant manager on 2/5/2010.

The NDA as resubmitted on 5/4/10 contained no changes to the CMC section of the application. At that point, only an acceptable overall OC recommendation was required to recommend approval from a chemistry viewpoint. A comprehensive GMP and pre-approval inspection (including laboratory operations), dated 10/18-22/2010, revealed that the firm has properly addressed the deficiencies noted during the previous pre-approval inspection. Specifically, the firm was found acceptable [redacted] (b) (4) covered by this NDA by the district office on 10/26/2010.

According to EES, an overall OC recommendation of acceptable for all manufacturing sites was made on 10/26/2010. Therefore, this application is now recommended for approval from an ONDQA viewpoint.

R/D Init by: Dr. P. Peri, Branch Chief, DNDQAIII, BVIII

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/s/

MARTIN T HABER
11/01/2010

PRASAD PERI
11/01/2010
I concur

NDA 22-450

Acetaminophen Injection

Cadence Pharmaceuticals, Inc.

Martin Haber, Ph.D.
Division of Pre-Marketing Assessment I

For
Division of Anesthesia, Analgesia and Rheumatology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 22 - 450

2. REVIEW #2

3. REVIEW DATE: September 9, 2010

4. REVIEWER: Martin Haber, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	5/12/2009
Amendment	6/19/2009
Amendment	8/12/2009
Amendment	9/14/2009
Chemistry Review #1	10/15/2009
Secondary Quality Review	10/19/2009
Addendum to Summary of the Basis for the Recommended Action from Chemistry, Manufacturing and Controls	2/10/2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	1/13/2010
Complete Resubmission	5/4/2010

7. NAME & ADDRESS OF APPLICANT:

Name: Cadence Pharmaceucticals, Inc

Address: 12481 High Bluff Drive, Suite 200, San Diego, CA 92130

Executive Summary Section

Representative: Tracy Ross-Teichert, Director, Regulatory Affairs

Telephone: 858-4361404

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Pending, various names proposed
b) Non-Proprietary Name (USAN): acetaminophen
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3 (new formulation/dosage form)
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: anti-pyretic and analgesic agent

11. DOSAGE FORM: Sterile aqueous solution for intravenous injection

12. STRENGTH/POTENCY: 1000 mg/100 mL

13. ROUTE OF ADMINISTRATION: Intravenous Injection

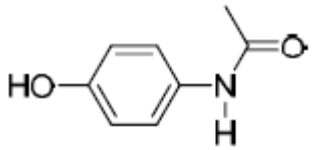
14. Rx/OTC DISPENSED: __x_Rx ___OTC

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:

Chemical Name(s):	N-acetyl-p-aminophenol
	4'-hydroxyacetanilide
	p-hydroxyacetanilide
	p-acetamidophenol
	p-acetaminophenol
	p-acetylaminophenol
Chemical Abstract Service (CAS):	103-90-2
USAN Name:	Acetaminophen
INN Name:	Paracetamol
Other Non-Proprietary Names:	APAP
Structural Formula:	
Molecular Formula:	$C_8H_9NO_2$
Molecular Weight:	151.16

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	Mallinckrodt	Acetaminophen	3	Adequate	7/7/2009	Reviewed by OGD
4681	III	Baxter	Parenteral Products	3	Adequate	10/13/2009	Reviewed by Microbiology

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF

3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	58,362	Clinical trials
NDA	21-123	Ultracet (acetaminophen)
NDA	19-872	Tylenol (acetaminophen extended release tablets)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Pharm/Tox	Acceptable	2/10/2010	C. K. Huynh
Microbiology	Acceptable	10/13/09	D. Miller

The Chemistry Review for NDA 22-450

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend Approval, pending a satisfactory facilities inspection evaluation

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

NA

II. Summary of Chemistry Assessments

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

The drug product, Acetaminophen Injection, is a clear sterile aqueous solution for injection containing 1000 mg of acetaminophen in 100 mL of solution (1% active, concentration 10 mg/mL). Each 100 mL vial also contains the following excipients: 3850 mg mannitol, 10.4 mg dibasic sodium phosphate, anhydrous and 25 mg cysteine hydrochloride, monohydrate. The solution pH is about 5.5 (b) (4)

The drug product is manufactured by Baxter Healthcare Corporation at their Cleveland, MS, site. The facility inspection EES report for this site regarding cGMP status is pending. The drug product is manufactured using standard techniques for sterile injectable solutions with extra efforts made to reduce oxygen content. In solution acetaminophen (b) (4) to the impurity 4-aminophenol, see discussion below.

(b) (4) Microbiology sterility assurance review dated 10/13/09 recommended approval from a quality microbiology standpoint.

Drug product specifications include identification, assay, impurities, cysteine, (b) (4) pH, osmolality, particulate matter and bacterial endotoxins. As requested by the Agency, tighter in-house limits for impurities and pH are in place for release, (b) (4) Cadence also agreed to tighten the shelf

life acceptance limits for the impurity 4-aminophenol to NMT (b) (4) and for pH (b) (4). Sterility is assured by parametric release requirements.

Stability studies demonstrated that during storage, (b) (4) acetaminophen occurs in solution to produce increasing amounts of the impurity, 4-aminophenol, with time. The amount of 4-aminophenol is (b) (4) at room temperature. In their 1/13/2010 Amendment, Cadence requested 18 months of expiry which is supported by 12 months of long term stability data at 25°C for 3 lots manufactured at their US production site. The limiting factor for shelf life is the allowed amount of 4-aminophenol at expiry, (b) (4)

The container/closure system is typical for an injectable product and consists of a cylindrical Type II clear glass vial of 100 mL nominal capacity, closed with a 32 mm dark grey (b) (4) rubber stopper and sealed with a 32 mm aluminum crimp with a blue plastic flip-off cap.

The drug substance, acetaminophen, is an antipyretic and analgesic agent. It is a well characterized compound that is the subject of EP and USP monographs. Acetaminophen was first approved by the FDA in 1951. Chemically, acetaminophen is the acetate amide of p-aminophenol, has a molecular weight of 151.16, and contains no chiral centers.

The drug substance is manufactured by Mallinckrodt, holder of DMF #5326, at their Raleigh, NC site. Most chemistry manufacturing information for the drug substance is referenced to this DMF. DMF #5326 has been reviewed numerous times by the Office of Generic Drugs and is adequate for this NDA. The facilities inspection EES report for this manufacturing site states that this site has an acceptable cGMP status as of 6/23/2009. As requested by the Agency, the NDA sponsor, Cadence, submitted drug substance specifications for this NDA which include tests for identification, assay, and impurities that include limits for total related substances and individual unidentified impurities. In general, reported batch data had assay levels that were high and impurity levels that were low. The mean amount of the impurity 4-aminophenol in drug substance batches was (b) and the specification limit is NMT (b) (4) (0.005%). ( )

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

The sterile drug product vials are for single use only and do not contain any (b) (4) preservative. The drug product should be administered only as a 15-minute intravenous infusion. The recommended dosage for adults over 50 kg is 650 - 1000 mg every 4 – 6 hours to a maximum dose of 4 g in 24 hours. Lower dosages are recommended for children (b) (4). The drug product is stored at controlled room temperature with an expiry of (b) (4). Adequate

primary stability data for 3 lots manufactured by Baxter and stored for 6 months was submitted in the 8/14/2009 Amendment to support the requested expiry. Submitted supportive stability data for lots manufactured in Italy and stored for 36 months also demonstrated adequate drug product stability.

C. Basis for Approvability or Not-Approval Recommendation

The NDA resubmission contained no changes to the CMC section of the application. The original NDA submission received a complete response action on 2/10/2010 because of a withhold approval recommendation for the drug product manufacturing facility, Baxter Healthcare Corporation, in Cleveland, MS. The withhold recommendation was made due to significant issues found during an inspection of the Baxter facility in January and February 2010. Specifically, as described in the Addendum to the Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls by Dr. P. Peri dated 2/10/10, the investigator found several unusual findings related to particulate matter in the registration stability batch and a form 483 was issued to the Baxter plant manager on 2/5/10. The current inspection status of this facility is pending.

III. Administrative

A. Reviewer's Signature

See DFS

B. Endorsement Block

See DFS

C. CC Block

See DFS

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/s/

MARTIN T HABER
09/22/2010

PRASAD PERI
09/22/2010
I concur

NDA 22-450

Acetaminophen Injection

Addendum to the Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Cadence Pharmaceuticals, Inc.

Indication: Treatment of acute pain and fever.

Presentation: The drug product will be packaged in a glass vial of 100 mL nominal capacity, closed with a 32 mm dark grey (b) (4) rubber stopper and sealed with a 32 mm aluminum crimp with a blue plastic flip-off cap.

EER Status:	Recommendations:	**Withhold as on Feb 10, 2010**
Consults:	EA –	Categorical exclusion provided
	CDRH-	N/A
	Statistics –	N/A
	Methods Validation –	Not recommended
	DMEPA-	Completed
	Biopharm–	N/A
	Microbiology –	Acceptable

Original Submission:	12-May-2009
Re-submissions:	N/A
Post-Approval CMC PMC/PMR:	None

Background:
Previous reviews for chemistry, manufacturing and controls (primary review by Dr. Martin Haber dated 10/15/2009 and Secondary review by Dr. Ali Al Hakim dated 10/19/2009) recommended that the application be approved. At that time, an acceptable recommendation dated 6/23/2009 was provided from the Office of Compliance. This recommendation was based in part on profile for the drug product manufacturing site: Baxter Healthcare Corporation, Cleveland, MS (CFN: 1019003).

Since that time, the district office has inspected the Baxter facility in Cleveland, MS on the following dates: 1/25/2010 to 2/5/2010. During the inspection, the investigator found several unusual findings related to particulate matter in the registration stability batch. For the registration stability batch V337112 at the 9th month time point large particulate matter were found in five of the samples. (b) (4) These particulates were found despite the fact that 100% of the drug product vials are examined visually for particulate matter after filling.

Baxter performed an investigation to identify the source of this contamination and their results concluded that the most probable cause of the particulate matter is cross contamination through personnel. Baxter indicates that their personnel were adequately retrained to minimize these cross contamination issues.

Details of additional GMP issues were listed and brought to the attention of the review Division (ONDQA, OND, and Quality Microbiology) and CDER Office of Compliance. These findings specifically for the current application, were summarized in form 483 and issued to Baxter plant manager by the investigators on 2/5/2010, including the following issues:

1. Control procedures are not established which validate the performance of those manufacturing process that may be responsible for causing variability in the characteristics of in-process material and the drug product.

2. Records are not kept for the maintenance and inspection of equipment.

3. Acceptance criteria for the sampling and testing conducted by the quality control unit is not adequate to assure that batches of drug products meet each appropriate specification as a condition for their approval and release.

Additional details of the issues were described in the draft form 483 that was shared with the extended review team.

CDER Office of Compliance found these issues to be significant and has issued a "withhold" recommendation for this site until all these issues are resolved satisfactorily.

Overall Conclusion:
From a CMC perspective, the application is **not recommended** for approval until the Office of Compliance recommends an overall acceptable status for the application.

Proposed draft language for the CR letter may be as follows:

During a recent inspection of the Baxter Healthcare manufacturing facility in Cleveland, MS for this application, our investigator conveyed deficiencies to the representative of the facility. Satisfactory compliance with Current Good Manufacturing Practices for Drugs is required for all manufacturing and testing facilities listed in the NDA before this application may be approved.

Prasad Peri, Ph.D.
Acting Branch Chief
DPA I/ONDQA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22450	ORIG-1	CADENCE PHARMACEUTICALS INC	Ofirmev (acetaminophen for injection)

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/s/

PRASAD PERI

02/10/2010

Changing recommendation from previous secondary review due to withhold status from the Office of Compliance

DATE: February 3, 2010

TO: NDA 22-450 Acetaminophen for Injection (Cadence Pharmaceuticals, Inc)

FROM: CMC Extended Review Team

SUBJECT: Internal Meeting on February 2, 2010 to Discuss Inspection of the Baxter facility in Cleveland, MS.

BACKGROUND: The Baxter facility (CFN: 1019003) located in Cleveland, MS has been identified as the drug product manufacturer for this application. The Establishment Evaluation Report (EER) was submitted and the facility was determined to be acceptable based on file review on October 7, 2009. In January 2010, the district office (DO) was conducting an inspection of the Baxter facility, when the Baxter representative informed the DO of the pending application for Cadence, for which the review clock was extended. As a result, the DO began a Pre-approval Inspection (PAI) for NDA 22-450. During the ongoing inspection, some observations were noted that may have impact on product quality. The DO contacted the CMC review team for the application to discuss their findings.

MEETING DISCUSSION:

The filling line for this product is a dedicated line and was recently installed. During the process validation activities, five batches were manufactured, and three of the batches met the acceptance criteria. The batches are summarized below.

Batch no.	**Summary**
V337108	Met validation criteria
V337109	Met validation criteria
V337110	Discarded (b) (4)
V337111	Discarded
V337112	Met validation criteria

The three batches submitted to the application as primary stability were V337108, V337109, V337112. These were also identified as the validation batches during the inspections. It was clear that even in the batches provided in the NDA, the manufacturing process was not consistent (b) (4)

The inspection also revealed that 8 additional batches were manufactured prior to the 5 batches listed above. All 8 batches failed validation criteria. According to the investigators, this was due to the fact that the equipment was a complicated piece of machinery and there were machine failures and operator errors. Adequate qualification of the installed equipment and adequate training of the operators may not have been done.

During the inspection, it was discovered that the 9-month stability testing for lot V337112 revealed a visible particulate matter (b) (4) This particulate matter was observed in five vials (b) (4). However, batch V337112 passed USP <788> particulate matter testing, and Cadence did not report any of these observations in the original NDA or the stability update submitted to the NDA on January 13, 2010. Baxter conducted an investigation which did not identify a definitive source of the particulate matter and concluded that the most probably cause of these were because of cross contamination from personnel in manufacturing. Re-training for the personnel involved in manufacturing is to be undertaken as a corrective action. Additionally, Baxter determined tha (b) (4)

Based on the above findings, the following concerns were expressed:

1. The Baxter manufacturing process has not produced a reproducible drug product of consistent quality. Ten of out of thirteen batches did not meet validation criteria and did not have the identical manufacturing process.
2. With the implementation of recent changes, the validation and primary stability batches will not be representative of the proposed commercial manufacturing process.
3. The validation batches have not been manufactured consecutively (GMP issue).

ACTION ITEMS:

NOTE: The goal date for this application is Feb 13, 2010

1. ONDQA will review DMF 4681 to determine whether the additional (b) (4) (b) (4) was submitted as an amendment.
2. DO will continue the inspection of the facility and provide recommendation to Compliance.
3. EER for the Baxter facility will be re-submitted.
4. Compliance will provide an overall recommendation for the establishments.
5. ONDQA will provide a final CMC recommendation for the application taking into account the new GMP recommendation by OC.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22450	ORIG-1	CADENCE PHARMACEUTICALS INC	Ofirmev (acetaminophen for injection)

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/s/

DON L HENRY
02/09/2010

PRASAD PERI
02/09/2010

NDA 22-450

Acetaminophen Injection

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Cadence Pharmaceuticals, Inc.

Indication: Treatment of acute pain and fever.

Presentation: The drug product will be packaged in a glass vial of 100 mL nominal capacity, closed with a 32 mm dark grey (b) (4) rubber stopper and sealed with a 32 mm aluminum crimp with a blue plastic flip-off cap.

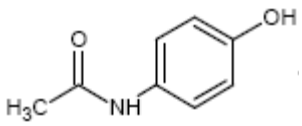
EER Status:	Recommendations:	Acceptable
Consults:	EA –	Categorical exclusion provided
	CDRH-	N/A
	Statistics –	N/A
	Methods Validation –	Not recommended
	DMEPA-	Completed
	Biopharm–	N/A
	Microbiology –	Acceptable

Original Submission:	12-May-2009
Re-submissions:	N/A
Post-Approval CMC PMC/PMR:	None

Background:
The application is filed as a 505(b)(2), priority NDA with 6-month review clock, based on the approved NDAs, Ultracet® (acetaminophen and tramadol) NDA 21-123 and Tylenol® (acetaminophen) NDA 19- 872. However, the applicant requested and granted priority review since there is an unmet medical need for injectable antipyretics in patients unable to take oral edications, including children.

Drug Substances:
The drug substance is manufactured by Mallinckrodt, holder of DMF #5326, at their Raleigh, NC site. Most chemistry manufacturing information for the drug substance is referenced to this DMF. DMF #5326 has been reviewed numerous times by the Office of Generic Drugs and is adequate for this NDA. The facilities inspection EES report for this manufacturing site states that this site has an acceptable cGMP status as of 6/23/2009. As requested by the Agency, the NDA sponsor, Cadence, submitted drug substance specifications for this NDA which include tests for identification, assay, and impurities that include limits for total related substances and individual unidentified impurities.

Chemical Name: N-acetyl-p-aminophenol
Structural Formula



Molecular Formula:
$C_8H_9NO_2$
Molecular Weight: 151.16
Conclusion: **T**he drug substance is satisfactory

Drug Product:

The drug product, Acetaminophen Injection, is a clear sterile aqueous solution for injection containing 1000 mg of acetaminophen in 100 mL of solution (1% active, concentration 10 mg/mL). Each 100 mL vial also contains 3850 mg mannitol, 10.4 mg dibasic sodium phosphate, anhydrous and 25 mg cysteine hydrochloride, monohydrate. Mannitol is added (b) (4) and cysteine is an antioxidant (b) (4)

The drug product solution is isotonic with blood having an osmolality of about 290 mOsm/kg. The solution pH is about 5.5 (b) (4) .
The drug product is manufactured by Baxter Healthcare Corporation at their Cleveland, MS, site. The drug product is manufactured using standard techniques for sterile injectable solutions (b) (4)

Acetaminophen also (b) (4) to the impurity 4- aminophenol, a potentially genotoxic impurity.
(b) (4)

(b) (4)

Drug product specifications include identification, assay, impurities, cysteine, (b) (4) pH, osmolality, particulate matter and bacterial endotoxins.

Stability studies demonstrated that during storage, (b) (4) acetaminophen occurs in solution to produce increasing amounts of the impurity, 4-aminophenol, with time. The amount of 4-aminophenol is (b) (4) at room temperature. Cadence requested and granted (b) (4) expiry which is supported by 6 months stability data at 25°C for 3 lots manufactured at their US production site and additional supportive stability data for 36 months at 25°C for lots manufactured in Italy.

Conclusion: The drug product is satisfactory.

Overall Conclusion:
From a CMC perspective, the application is recommended for approval.

Ali Al-Hakim, Ph.D.
Branch Chief
DPA I/ONDQA

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22450	ORIG-1	CADENCE PHARMACEUTICALS INC	ACETAMINOPHEN FOR INJECTION FOR IV USE

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/s/

ALI H AL HAKIM
10/19/2009

NDA 22-450

Acetaminophen Injection

Cadence Pharmaceuticals, Inc.

Martin Haber, Ph.D.
Division of Pre-Marketing Assessment I

For
Division of Anesthesia, Analgesia and Rheumatology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-450

2. REVIEW #1

3. REVIEW DATE: October 14, 2009

4. REVIEWER: Martin Haber, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NA	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	5/12/2009
Amendment	6/19/2009
Amendment	8/12/2009
Amendment	9/14/2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Cadence Pharmaceucticals, Inc
Address:	12481 High Bluff Drive, Suite 200, San Diego, CA 92130
Representative:	Tracy Ross-Teichert, Director, Regulatory Affairs
Telephone:	858-4361404

8. DRUG PRODUCT NAME/CODE/TYPE:

Executive Summary Section

a) Proprietary Name: Various names proposed (Acetavance, [redacted], others etc., final decision is pending)
b) Non-Proprietary Name (USAN): acetaminophen
c) Code Name/# (ONDC only): NA
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3 (new formulation and dosage form)
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: anti-pyretic and analgesic agent

11. DOSAGE FORM: Sterile aqueous solution for intravenous injection

12. STRENGTH/POTENCY: 1000 mg/100 mL

13. ROUTE OF ADMINISTRATION: Intravenous Injection

14. Rx/OTC DISPENSED: __x_Rx ___OTC

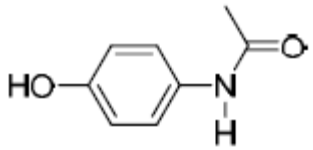
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

x SPOTS product – Form Completed (Excipient: Cysteine [redacted])

_____Not a SPOTS product

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

Executive Summary Section

Chemical Name(s):	N-acetyl-p-aminophenol 4'-hydroxyacetanilide p-hydroxyacetanilide p-acetamidophenol p-acetaminophenol p-acetylaminophenol
Chemical Abstract Service (CAS):	103-90-2
USAN Name:	Acetaminophen
INN Name:	Paracetamol
Other Non-Proprietary Names:	APAP
Structural Formula:	
Molecular Formula:	$C_8H_9NO_2$
Molecular Weight:	151.16

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
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4681	III	Baxter	Parenteral Products	3	Adequate	10/13/2009	Reviewed by Microbiology

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B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	58,362	Clinical trials
NDA	21-123	Ultracet (acetaminophen)
NDA	19-872	Tylenol (acetaminophen extended release tablets)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	10/7/09	
Methods Validation	Not required		M. Haber
EA	Exclusion requested and acceptable		M. Haber
Microbiology	Acceptable	10/13/09	D. Miller

The Chemistry Review for NDA 22-450

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend Approval

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

NA

II. Summary of Chemistry Assessments

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

The drug product, Acetaminophen Injection, is a clear sterile aqueous solution for injection containing 1000 mg of acetaminophen in 100 mL of solution (1% active, concentration 10 mg/mL). The drug product is indicated for the treatment of acute pain and fever. Each 100 mL vial also contains the following excipients: 3850 mg mannitol, 10.4 mg dibasic sodium phosphate, anhydrous and 25 mg cysteine hydrochloride, monohydrate. Mannitol is added (b) (4) and cysteine is an antioxidant added (b) (4). The drug product solution is isotonic with blood having an osmolality of about 290 mOsm/kg. The solution pH is about 5.5 (b) (4)

The drug product is manufactured by Baxter Healthcare Corporation at their Cleveland, MS, site. The facility inspection EES report for this site regarding cGMP status was acceptable as of 10/7/2009. The drug product is manufactured using standard techniques for sterile injectable solutions (b) (4) Acetaminophen also (b) (4) to the impurity 4-aminophenol, a potentially genotoxic impurity, see discussion below.

(b) (4)

(b) (4). Microbiology sterility assurance review dated 10/13/09 recommended approval from a quality microbiology standpoint.

Drug product specifications include identification, assay, impurities, cysteine, (b) (4) pH, osmolality, particulate matter and bacterial endotoxins. As requested by the Agency, tighter in-house limits for impurities and pH are in place for release, (b) (4). Cadence also agreed to tighten the shelf life acceptance limits for the impurity 4-aminophenol to NMT (b) (4) and for pH (b) (4). Sterility is assured by parametric release requirements.

Stability studies demonstrated that during storage, (b) (4) acetaminophen occurs in solution to produce increasing amounts of the impurity, 4-aminophenol, with time. The amount of 4-aminophenol is (b) (4) at room temperature. Cadence is requesting (b) (4) of expiry which is supported by 6 months of long term stability data at 25°C for 3 lots manufactured at their US production site. Supportive stability data for 36 months at 25°C for lots manufactured in Italy was also provided. The limiting factor for shelf life is the allowed amount of 4-aminophenol at expiry, (b) (4).

Note: In response to a request from the Agency in the 74-day letter dated 7/22/2009, the firm submitted a toxicological risk assessment regarding the safety of 4-aminophenol in an 8/13/2009 Amendment. The risk assessment asserts that the maximum proposed level of 4-aminophenol in both drug substance and product is safe for human use. This assessment will be evaluated by the pharmacology toxicology review team.

The container/closure system is typical for an injectable product and consists of a cylindrical Type II clear glass vial of 100 mL nominal capacity, closed with a 32 mm dark grey (b) (4) rubber stopper and sealed with a 32 mm aluminum crimp with a blue plastic flip-off cap.

The drug substance, acetaminophen, is an antipyretic and analgesic agent. It is a well characterized compound that is the subject of EP and USP monographs. Acetaminophen was first approved by the FDA in 1951. Chemically, acetaminophen is the acetate amide of p-aminophenol, has a molecular weight of 151.16, and contains no chiral centers.

The drug substance is manufactured by Mallinckrodt, holder of DMF #5326, at their Raleigh, NC site. Most chemistry manufacturing information for the drug substance is referenced to this DMF. DMF #5326 has been reviewed numerous times by the Office of Generic Drugs and is adequate for this NDA. The facilities inspection EES report for this manufacturing site states that this site has an acceptable cGMP status as of 6/23/2009. As requested by the Agency, the NDA

sponsor, Cadence, submitted drug substance specifications for this NDA which include tests for identification, assay, and impurities that include limits for total related substances and individual unidentified impurities. In general, reported batch data had assay levels that were high and impurity levels that were low. The mean amount of the impurity 4-aminophenol in drug substance batches was (b) (4) and the specification limit is NMT (b) (4)

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

The sterile drug product vials are for single use only and do not contain any (b) (4) preservative. The drug product should be administered only as a 15-minute intravenous infusion. The recommended dosage for adults over 50 kg is 650 - 1000 mg every 4 – 6 hours to a maximum dose of 4 g in 24 hours. Lower dosages are recommended for children (b) (4) The drug product is stored at controlled room temperature with an expiry of (b) (4) Adequate primary stability data for 3 lots manufactured by Baxter and stored for 6 months was submitted in the 8/14/2009 Amendment to support the requested expiry. Submitted supportive stability data for lots manufactured in Italy and stored for 36 months also demonstrated adequate drug product stability.

C. Basis for Approvability or Not-Approval Recommendation

The firm has adequately responded (8/13/2009 and 9/14/2009 Amendments) to all chemistry deficiencies described in the 74-day letter and a 9/1/2009 IR letter. The NDA received an EES overall recommendation of acceptable on 10/7/2009. There are no pending chemistry issues.

III. Administrative

A. Reviewer's Signature

See DFS

B. Endorsement Block

See DFS

C. CC Block

See DFS

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22450	ORIG-1	CADENCE PHARMACEUTICALS INC	ACETAMINOPHEN FOR INJECTION FOR IV USE

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

/s/

MARTIN T HABER
10/15/2009

ALI H AL HAKIM
10/15/2009

Initial Quality Assessment
Division of Pre-Marketing Assessment I, Branch II
Office of New Drug Quality Assessment
Division of Anesthesia, Analgesia and Rheumatology Products

OND Division:	Anesthesia, Analgesia and Rheumatology	
NDA:	22-450	
Applicant:	Cadence Pharmaceuticals	
Stamp date:	May 13, 2008	
PDUFA Date:	November 13, 2009	
Trademark:	ACETAVANCE™	
Established Name:	Acetaminophen Injection	
Dosage Form:	Intravenous Injection, 10 mg/ml	
Route of Administration:	Parenteral (IV)	
Indication:	Treatment of acute pain; reduction in fever in adults and children	
Pharmaceutical Assessment Lead:	Danae D. Christodoulou, Ph.D.	
	YES	NO
ONDQA Fileability:	√	___
Comments for 74-Day Letter:	√	___

Summary, Critical Issues and Comments

A. Summary

The application is filed as a 505(b)(2), priority NDA with 6-month review clock, based on the approved NDAs, Ultracet® (acetaminophen and tramadol) NDA 21-123 and Tylenol® (acetaminophen) NDA 19-872. In addition, the application relies on the Monograph for OTC Internal Analgesic, Antipyretic, and Antirheumatic Drug Products, published literature, as well as data developed by the applicant. The applicant requested priority review since there is an unmet medical need for injectable antipyretics in patients unable to take oral medications, including children.

Acetaminophen is a non-salicylate antipyretic and non-opioid analgesic agent. Oral acetaminophen was approved in the US originally in 1951, as children's Tylenol® in 1955 and OTC product in 1960. The IV formulation was approved for use in France as Perfalgan®, currently marketed by BMS in 80 countries. Cadence licensed in 2006 the North American development of IV acetaminophen. The proposed Acetavance™ formulation is identical to that of Perfalgan®. With the exception of the recently approved Caldolor® (ibuprofen IV injection), no other intravenous antipyretic medications are currently approved in the US.

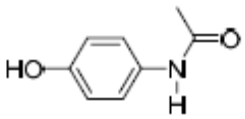
The drug substance, acetaminophen, is manufactured by Mallinkrodt, and referenced to the Drug Master File (DMF) 5326. A Letter of Authorization (LoA) has been provided.

The drug product is formulated as a sterile aqueous solution for injection, 10 mg/ml, in 100 ml USP Type II glass vials and sealed with dark grey (b) (4) rubber stoppers and aluminum crimp with plastic flip-off caps. The drug product is manufactured by Baxter, (b) (4) Based on 24-36 month real time stability data on clinical and supporting batches, and three month data on primary batches manufactured at the proposed commercial manufacturing site, a 12-month expiry date is proposed.

B. Review, Comments and Recommendations

Drug Substance Acetaminophen

Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight



Chemical Name(s): N-acetyl-p-aminophenol, 4'-hydroxyacetanilide, p-hydroxyacetanilide, p-acetamidophenol, p-acetaminophenol, p-acetylaminophenol
USAN Name: Acetaminophen
INN Name: Paracetamol
Other Non-Proprietary Names: APAP
Molecular formula: $C_8H_9NO_2$
Molecular weight: 151.16

As discussed above, acetaminophen is manufactured by Mallinkrodt, Cleveland, as a white crystalline powder and referenced to DMF 5326. Specifications of impurities are based on the USP monograph. Details regarding the manufacturing process, characterization and impurities are referenced to DMF 5326. This DMF should be assessed for the manufacturing process, controls and stability data (retest date (b) (4) that support acetaminophen. The drug substance specifications should be assessed as per ICH Q3A(R2) in consultation with the Toxicology division. (b) (4)

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C. Critical issues for review and recommendation

During assessment of the CMC information provided in this NDA, the primary reviewer should consider addressing issues identified above and other related ones, summarized here, for their impact on drug product quality and performance throughout the shelf-life:

1. The drug substance DMF 5326 should be assessed. The process capability with respect to levels of the impurity 4-amonophenol should be assessed and whether the proposed specification (b) (4) is the lowest achievable.
2. Suitability of the proposed drug substance specifications for acetaminophen should be assessed as per ICH Q3(R) and ICH Q3B(R), in consultation with the Toxicology division.
3. Suitability of the manufacturing process, for the drug product, which includes (b) (4) sterilization, should be assessed in consultation with the Microbiology division. In addition, specifications, microbiolgical integrity of the closures, and comparisons of the processes between manufacturing sites should be evaluated accordingly.
4. (b) (4) manufacturing conditions should be assessed.
5. The Baxter DMF 4681 should be assessed. All information regarding compatibility of the packaging system including the leachables/extractables evaluation should be assessed in consultation with the Toxicology division.
6. Method Validation for the non-compendial methods (HPLC, TLC) for the drug product.
7. Compatibility of the drug product with common diluents and drugs. Note that the applicant did not provide chemical assessment of compatibility.
8. Specifications (in-process and end product testing) for critical attributes of the drug product, e.g., pH, osmolality, cysteine and mannitol assays, etc.
9. Specifications for drug product impurities/degradants as discussed in 2 above for the drug substance.
10. Proposed expiration dating (b) (4), including storage orientations, conditions of storage and statistical analysis evaluation. The applicant should be asked to justify the choice of low humidity conditions and provide post-approval stability data under ICH standard conditions.

D. Comment for the 74-day Letter:

1. Provide a stability update with updated summary for the primary batches V337108, V337109 and V337112, manufactured at Baxter. In addition, provide a justification for the choice of (b) (4) storage conditions, and a commitment to place post-approval batches on standard ICH long term conditions.

E. Recommendation for fileability:

The NDA is fileable based on sufficient number of primary stability and supporting batches, and 24 month real time stability data on clinical batches at 25°C/40% RH. The NDA is suitable for evaluation and assessment based on FDA and ICH guidelines for submitting CMC information for New Drug Applications.

Recommendation for Team Review: The NDA is not recommended for team review. The drug substance is not an NME, the formulation does not include novel excipients and the manufacturing process for the drug product does not present complexity, e.g., novel delivery or device issues, nor significant development. In addition, the primary stability and clinical batches are representative of the commercial process.

Consults:

Since the ACETAVANCE™ product is an injectable, microbiology consult is required and was initiated.

Specifications for impurities and leachables/extractables evaluation should be assessed in consultation with the Toxicology reviewer.

Statistical analysis consult was not deemed necessary, since a significant body of real time data has been included in the NDA and the applicant limited shelf life based on their statistical analysis evaluation.

Danae D Christodoulou, Ph.D.	7/9/2009
Pharmaceutical Assessment Lead	Date
Ali Al-Hakim, Ph.D.	7/9/2009
Branch II Chief, ONDQA	Date

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		Categorical exclusion requested 21CFR 25.31(a)
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		Stability data have been provided with statistical analysis
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	NA		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		Injectable
16	Have all consults been identified and initiated?	√ N/A N/A N/A N/A √		Pharm/Tox Statistics OCP/CDRH/CBER LNC DMETS/ODS Microbiology

Have all DMF References been identified? Yes (√) No ( )

DMF Number	Holder	Description	LoA Included	Status
5326 Type II	Covidien (Mallinkrodt) 675 McDonnell Boulevard, Hazelwood, MO	Acetaminophen USP	Yes	pending
4681* Type III	Baxter Healthcare Corporation 1620 Waukegan Road McGaw Park, IL	Production of Parenteral (b) (4)	Yes	pending

(b) (4)

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

/s/

Danae Christodoulou
7/9/2009 04:22:39 PM
CHEMIST

Ali Al-Hakim
7/9/2009 05:00:00 PM
CHEMIST