

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202088Orig1s000

CHEMISTRY REVIEW(S)

NDA 202088

TRADENAME¹

(phentermine HCl) **Orally Disintegrating Tablet**

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

Applicant: Citius Pharmaceuticals, LLC
63 Great Road,
Maynard,
MA 01754

Indication: Treatment of Obesity

Presentation: The drug product will be packaged in high density polyethylene (HDPE) 30-count and 100-count bottles with a child-resistant closure and a desiccant.

Establishments Evaluation Report (EER) Status: **Acceptable**

Consults:	EA -	Acceptable
	Statistics -	N/A
	Methods Validation -	Not requested
	Clinical Pharm -	N/A
	Microbiology -	N/A
	Pharm Toxicology -	N/A

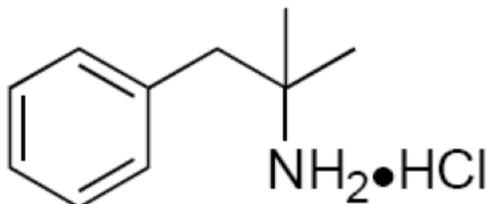
Original Submission:	August 11, 2010
Re-submissions:	N/A
Post-Approval CMC Agreements:	None at this time.

Drug Substance

The drug substance, phentermine HCl, is a previously approved drug substance, produced by chemical synthesis.

¹ To be determined.

Chemical structure, chemical name, molecular formula and molecular weight are shown below:



Phentermine HCl

Chemical name: α,α -Dimethylphenethylamine hydrochloride
Molecular Formula: $C_{10}H_{15}N \cdot HCl$
Molecular Weight: 185.7 g/mol

Phentermine hydrochloride is a white, odorless, hygroscopic, crystalline powder which is soluble in water and lower alcohols, slightly soluble in chloroform and insoluble in ether. All information regarding the physicochemical properties, impurities, method of synthesis and purification, process controls, control of raw materials, container closure system and stability of phentermine HCl are provided in the Drug Master File (DMF) (b) (4) held by (b) (4). DMF (b) (4) was reviewed and found adequate to support an ANDA for an orally administered tablet. The drug substance specifications are the same as the USP monograph for phentermine HCl, with the addition of Organic Volatile Impurities, Residual Solvents, Assay by HPLC, Solution in ethanol (% transmission, color, clarity), Solution in water (color, clarity), and Impurities.

The drug substance phentermine HCl will be manufactured by (b) (4). The retest period for phentermine HCl is (b) (4) when stored in the (b) (4) at room temperature conditions.

Drug substance is satisfactory

Drug product

The proposed drug product is an orally disintegrating tablet (ODT) containing 15, 30 (b) (4) mg of phentermine hydrochloride (equivalent to 12, 24 (b) (4) mg of phentermine base).

The (b) (4) steps involve in the manufacturing process of the drug product tablets (ODT) are (b) (4).

The drug product contains the inactive ingredients mannitol powder, citric acid powder, Povidone CL, Povidone K 30, sucralose, magnesium stearate, peppermint flavor, talc, sodium lauryl sulfate, and mannitol pregranulated. The

15 mg ODT also contains FD&C Blue # 1 lake and FD&C Yellow # 5 lake. The 30 mg ODT also contains FD&C Yellow # 5 lake (b) (4)

The applicant proposes the following labeling statements: (b) (4)

Drug product specifications include appearance, odor, disintegration time, thickness, diameter, moisture, dissolution, Assay and identification of phentermine, uniformity of dosage units, related substances/impurities and microbial limits.

The provided stability data provided in the NDA support an expiry dating period of 24 months.

Drug product is satisfactory

Overall Conclusion:

From the CMC point of view, the application is recommended for APPROVAL.

Ali Al-Hakim, Ph.D.
Branch Chief, Division III
ONDQA/CDRR/FDA

Proposed label for the 15 mg tablet



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/s/

ALI H AL HAKIM
05/12/2011

NDA 202-088

TRADENAM*
(phentermine HCl)
Orally Disintegrating Tablet

Citius Pharmaceuticals, LLC

Elsbeth Chikhale, Ph.D.
ONDQA – Div III – Branch VII

for
Division of Metabolism and Endocrinology Products

*** To be determined**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments	7
A. Description of the Drug Product(s) and Drug Substance(s).....	7
B. Description of How the Drug Product is Intended to be Used	7
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative.....	8
A. Reviewer's Signature.....	8
B. Endorsement Block.....	8
C. CC Block	8
Chemistry Assessment	9
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	9
S DRUG SUBSTANCE [Phentermine HCl, (b) (4).....	9
P DRUG PRODUCT [Tradename, Tablet]	9
A APPENDICES	19
R REGIONAL INFORMATION	19
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	19
A. Labeling & Package Insert	19
B. Environmental Assessment Or Claim Of Categorical Exclusion	19
III. List Of Information Requests Communicated	N/A

Chemistry Review Data Sheet

1. NDA 202-088
2. REVIEW #: 2
3. REVIEW DATE: 9-MAY-2011
4. REVIEWER: Elsbeth Chikhale, Ph.D.
5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed:	Document Date:
Original	11-AUG-2010
Amendment to original ¹	11-OCT-2010
Amendment to original ²	12-OCT-2010
Amendment to original ³	28-OCT-2010
Amendment to original ⁴	15-NOV-2010
Amendment to original ⁵	17-NOV-2010
Amendment to original ⁶	29-DEC-2010
Amendment to original ⁷	18-FEB-2011
Amendment to original ⁸	25-MAR-2011
Amendment to original ⁹	13-APR-2011

- 1) The 10/11/10 amendment provides for a response to the CMC IR dated 8/25/10
- 2) The 10/12/10 amendment provides for a response to the IR dated 10/4/10
- 3) The 10/28/10 amendment provides for updated stability data
- 4) The 11/15/10 amendment provides for electronic files of the original NDA CMC sections
- 5) The 11/17/10 amendment provides for a response to the IR dated 10/26/10
- 6) The 12/29/10 amendment provides for updated stability data
- 7) The 2/18/11 amendment provides for a response to the IR dated 2/8/11
- 8) The 3/25/11 amendment provides for updated stability data
- 9) The 4/13/11 amendment provides for a correction to the 2/18/11 amendment

7. NAME & ADDRESS OF APPLICANT:

Name:	Citius Pharmaceuticals, LLC
Address:	63 Great Road, Maynard, MA 01754
Contact person:	Steven Kates, Ph.D., Vice President
Telephone:	(678) 938-0338

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Tradename™
b) Non-Proprietary Name (USAN): Phentermine HCl
c) Code Name/#:
d) Chem. Type/Submission Priority:
- Chem. Type: 3 (New Dosage Form)
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(2) application. The reference drugs are: (b) (4) Phentermine HCl Capsules, 30 mg and 15 mg (Sandoz).

10. PHARMACOL. CATEGORY:

Phentermine HCl is a sympathomimetic amine anorectic.

11. DOSAGE FORM: Orally Disintegrating Tablet (ODT)

12. STRENGTH/POTENCY: 15 mg/tablet
30 mg/tablet
(b) (4)

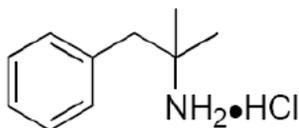
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product Form Completed
 Not a SPOTS product

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

Phentermine HCl:

Chemistry Review Data Sheet

Chemical name: α,α -Dimethylphenethylamine hydrochloride
 CAS registration number: 1197-21-3
 Molecular Formula: C₁₀H₁₅N·HCl
 Molecular Weight: 185.7 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Phentermine HCl, Drug substance	3	Adequate	June 9, 2010	Reviewed by S. Basaran, Ph.D.

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 relevant revision since last review

4 Sufficient information in application

5 Authority to reference not granted

6 DMF not available

7 Other

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	76,477	Orally Disintegrating Tablets, Citius Pharmaceuticals LLC

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biopharmaceutics	Drug product dissolution acceptance criteria changed to NLT (b) (4) in 15 minutes	1/26/11	Tapash Gosh, Ph.D.
Biometrics	N/A		
EES	Acceptable	4/13/10	
Pharm/Tox	N/A		
CDRH	N/A		
Clinical Pharmacology	N/A		
Methods Validation	FDA revalidation is not needed	2/2/11	Review #1 Elsbeth Chikhale, Ph.D.
DMEPA	Pending		
DDMAC	Pending		
EA	Categorical exclusion granted (consult not needed)	2/2/11	Review #1 Elsbeth Chikhale, Ph.D.
Microbiology	N/A		

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 202-088

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view, the application is recommended for APPROVAL. The provided stability data support an expiry dating period of 24 months (b) (4). Final labeling will be done in coordination with the clinical division.

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 and Drug Substances

1) Drug Product

The proposed drug product is an orally disintegrating tablet containing 15, 30 (b) (4) (b) (4) mg of phentermine hydrochloride (equivalent to 12, 24 (b) (4) mg of phentermine base). The drug product contains the inactive ingredients mannitol powder, citric acid powder, Povidone CL, Povidone K 30, sucralose, magnesium stearate, peppermint flavor, talc, sodium lauryl sulfate, and mannitol pregranulated. The 15 mg ODT also contains FD&C Blue # 1 lake and FD&C Yellow # 5 lake. The 30 mg ODT also contains FD&C Yellow # 5 lake (b) (4). The provided stability data support an expiry dating period of 24 months (b) (4). The drug product will be manufactured by Alpex PHARMA SA, Switzerland. The drug product will be packaged in high-density polyethylene (HDPE) 30-count and 100-count bottles with a child-resistant closure with desiccant.

2) Drug Substance: Phentermine HCl:

The drug substance, phentermine HCl, is a previously approved drug substance, produced by chemical synthesis. Phentermine hydrochloride is white, odorless, hygroscopic, crystalline powder which is soluble in water and lower alcohols, slightly soluble in chloroform and insoluble in ether. All information regarding the physicochemical properties, impurities, method of synthesis and purification,

process controls, control of raw materials, container closure system and stability of phentermine HCl are provided in the Drug Master File (DMF) (b) (4) held by (b) (4). DMF (b) (4) was reviewed on 6/9/10 (review #13 by S. Basaran, Ph.D.) and found adequate to support an ANDA for an orally administered tablet. The drug substance specifications are the same as the USP monograph for phentermine HCl, with the addition of Organic Volatile Impurities, Residual Solvents, Assay by HPLC, Solution in ethanol (% transmission, color, clarity), Solution in water (color, clarity), and Impurities. The drug substance phentermine HCl will be manufactured by (b) (4). The retest period for phentermine HCl is (b) (4) when stored in the (b) (4) described in DMF (b) (4) at room temperature conditions.

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

The drug product is indicated as a short-term (a few weeks) adjunct in a regimen of weight reduction based on exercise, behavioral modification and caloric restriction in the management of exogenous obesity for patients with an initial body mass index ≥ 30 kg/m², or ≥ 27 kg/m² in the presence of other risk factors (e.g., hypertension, diabetes, hyperlipidemia). The drug product contains phentermine hydrochloride, which is a schedule IV controlled substance. The drug product dosage should be individualized to obtain an adequate response with the lowest effective dose. The usual adult dose is one tablet daily as prescribed by the physician, administered (b) (4). Late evening medication should be avoided because of the possibility of resulting insomnia. The applicant proposes the following labeling statements: (b) (4)

(b) (4) Labeling changes to these directions will be discussed during the labeling review with the entire review team.

C. Basis for Approvability or Not-Approval Recommendation

From the CMC point of view, the application is recommended for APPROVAL. The provided stability data support an expiry dating period of 24 months (b) (4).

III. Administrative

- A. Reviewer's Signature: in DARRTS
- B. Endorsement Block: in DARRTS
- C. cc Block: in DARRTS

11 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

ELSBETH G CHIKHALE
05/09/2011

ALI H AL HAKIM
05/09/2011

NDA 202-088

**TRADENAME™
(phentermine HCl)
Orally Disintegrating Tablet**

Citius Pharmaceuticals, LLC

**Elsbeth Chikhale, Ph.D.
ONDQA – Div III – Branch VII**

**for
Division of Metabolism and Endocrinology Products**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments	7
A. Description of the Drug Product(s) and Drug Substance(s).....	7
B. Description of How the Drug Product is Intended to be Used	8
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative.....	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
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Chemistry Assessment	10
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	10
S DRUG SUBSTANCE [Phentermine HCl, (b) (4).....	10
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B. Environmental Assessment Or Claim Of Categorical Exclusion	44
III. List Of Information Requests Communicated	45

Chemistry Review Data Sheet

1. NDA 202-088
2. REVIEW #: 1
3. REVIEW DATE: 2-FEB-2011
4. REVIEWER: Elsbeth Chikhale, Ph.D.
5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed:	Document Date:
Original	11-AUG-2010
Amendment to original ¹	11-OCT-2010
Amendment to original ²	12-OCT-2010
Amendment to original ³	28-OCT-2010
Amendment to original ⁴	15-NOV-2010
Amendment to original ⁵	17-NOV-2010
Amendment to original ⁶	29-DEC-2010

- 1) The 10/11/10 amendment provides for a response to the CMC IR dated 8/25/10
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- 3) The 10/28/10 amendment provides for updated stability data
- 4) The 11/15/10 amendment provides for electronic files of the original NDA CMC sections
- 5) The 11/17/10 amendment provides for a response to the IR dated 10/26/10
- 6) The 12/29/10 amendment provides for updated stability data

7. NAME & ADDRESS OF APPLICANT:

Name:	Citius Pharmaceuticals, LLC
Address:	63 Great Road, Maynard, MA 01754
Contact person:	Steven Kates, Ph.D., Vice President
Telephone:	(678) 938-0338

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Tradename™
- b) Non-Proprietary Name (USAN): Phentermine HCl
- c) Code Name/#:

Chemistry Review Data Sheet

d) Chem. Type/Submission Priority:

- Chem. Type: 3 (New Dosage Form)
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(2) application. The reference drugs are: (b) (4) Phentermine HCl Capsules, 30 mg and 15 mg (Sandoz).

10. PHARMACOL. CATEGORY:

Phentermine HCl is a sympathomimetic amine anorectic.

11. DOSAGE FORM: Orally Disintegrating Tablet (ODT)

12. STRENGTH/POTENCY: 15 mg/tablet
30 mg/tablet
(b) (4)

13. ROUTE OF ADMINISTRATION: Oral

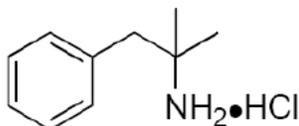
14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product Form Completed
 Not a SPOTS product

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

Phentermine HCl:



Chemical name: α,α -Dimethylphenethylamine hydrochloride

CAS registration number: 1197-21-3

Molecular Formula: $C_{10}H_{15}N \cdot HCl$

Molecular Weight: 185.7 g/mol

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Phentermine HCl, Drug substance	3	Adequate	June 9, 2010	Reviewed by S. Basaran, Ph.D.

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 relevant revision since last review

4 Sufficient information in application

5 Authority to reference not granted

6 DMF not available

7 Other

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	76,477	Orally Disintegrating Tablets, Citius Pharmaceuticals LLC

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biopharmaceutics	Drug product dissolution acceptance criteria changed to NLT (b) (4) in 15 minutes	1/26/11	Tapash Gosh, Ph.D.
Biometrics	N/A		
EES	Pending	2/9/10	
Pharm/Tox	N/A		
CDRH	N/A		
Clinical Pharmacology	N/A		
Methods Validation	FDA revalidation is not needed	2/2/11	Elsbeth Chikhale, Ph.D.
DMEPA	Pending		
DDMAC	Pending		
EA	Categorical exclusion granted (consult not needed)	2/2/11	Elsbeth Chikhale, Ph.D.
Microbiology	N/A		

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 202-088

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view, the recommendation for this application is pending:

- Submission of additional stability data (expected in April 2011) and review of the stability data.
- Overall recommendation from the Office of Compliance regarding the cGMP status of the manufacturing and testing facilities.
- Acceptable responses to the information requests noted at the end of this review (pg.45).

Final labeling will be done in coordination with the clinical division.

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 and Drug Substances

1) Drug Product

The proposed drug product is an orally disintegrating tablet containing 15, 30 (b) (4) (b) (4) mg of phentermine hydrochloride (equivalent to 12, 24 (b) (4) mg of phentermine base). The drug product contains the inactive ingredients mannitol powder, citric acid powder, Povidone CL, Povidone K 30, sucralose, magnesium stearate, peppermint flavor, talc, sodium lauryl sulfate, and mannitol pregranulated. The 15 mg ODT also contains FD&C Blue # 1 lake and FD&C Yellow # 5 lake. The 30 mg ODT also contains FD&C Yellow # 5 lake (b) (4). The stability data are incomplete at this time and will be updated in April 2011, as indicated in the amendment dated December 29, 2010. The stability data will be reviewed in review #2 and based on the provided data, an expiry dating period will be determined accordingly. The drug product will be manufactured by AlpeX PHARMA SA, Switzerland. The drug product will be packaged in high-density polyethylene (HDPE) 30-count and 100-count bottles with a child-resistant closure with desiccant.

2) Drug Substance: Metformin HCl:

The drug substance, phentermine HCl, is a previously approved drug substance, produced by chemical synthesis. Phentermine hydrochloride is white, odorless, hygroscopic, crystalline powder which is soluble in water and lower alcohols, slightly soluble in chloroform and insoluble in ether. All information regarding the physicochemical properties, impurities, method of synthesis and purification, process controls, control of raw materials, container closure system and stability of phentermine HCl are provided in the Drug Master File (DMF) (b) (4) held by (b) (4). DMF (b) (4) was reviewed on 6/9/10 (review #13 by S. Basaran, Ph.D.) and found adequate to support an ANDA for an orally administered tablet. The drug substance specifications are the same as the USP monograph for phentermine HCl, with the addition of Organic Volatile Impurities, Residual Solvents, Assay by HPLC, Solution in ethanol (% transmission, color, clarity), Solution in water (color, clarity), and Impurities. The drug substance phentermine HCl will be manufactured by (b) (4). (b) (4) The retest period for phentermine HCl is (b) (4) when stored in the (b) (4) described in DMF (b) (4) at room temperature conditions.

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

The drug product is indicated as a short-term (a few weeks) adjunct in a regimen of weight reduction based on exercise, behavioral modification and caloric restriction in the management of exogenous obesity for patients with an initial body mass index ≥ 30 kg/m², or ≥ 27 kg/m² in the presence of other risk factors (e.g., hypertension, diabetes, hyperlipidemia). The drug product contains phentermine hydrochloride, which is a schedule IV controlled substance. The drug product dosage should be individualized to obtain an adequate response with the lowest effective dose. The usual adult dose is one tablet daily as prescribed by the physician, administered (b) (4). Late evening medication should be avoided because of the possibility of resulting insomnia. The applicant proposes the following labeling statements: (b) (4)

(b) (4)

C. Basis for Approvability or Not-Approval Recommendation

From the CMC point of view, the recommendation is pending and will be finalized in review #2.

III. Administrative

- A. **Reviewer's Signature:** in DARRTS
- B. **Endorsement Block:** in DARRTS
- C. **cc Block:** in DARRTS

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/s/

ELSBETH G CHIKHALE
02/02/2011

ALI H AL HAKIM
02/02/2011

Initial Quality/CMC Assessment
ONDQA

Division of Metabolism and Endocrinology Products

NDA: 202088

Applicant: Citius Pharmaceuticals LLC

Stamp Date: 17-AUG-2010

PDUFA Date: 17-JUN-2011

Proposed Proprietary Name: (b) (4)

Established Name: Phentermine hydrochloride

Dosage form and strength: Orally disintegrating tablet
15, 30, (b) (4) mg

Route of Administration: Oral administration

Indications: Treatment of obesity

CMC Lead: Su (Suong) Tran, ONDQA

ONDQA Fileability: Yes

Initial Quality/CMC Assessment
ONDQA

CONSULTS/ CMC RELATED REVIEWS	COMMENT
CBER	<i>Not applicable</i>
CDRH	<i>Not applicable</i>
EA	The categorical exclusion claim cites a nonexistent regulation; see the 74-day comment. The applicant's response will be assessed by Primary Reviewer.
Compliance (DMPQ)	EER was sent to Compliance by ONDQA PM on 31-AUG-2010.
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
Microbiology	Review of microbial limits.
OBP	<i>Not applicable</i>
ONDQA Biopharm	Review of all dissolution/drug release-related information (and biowaiver information, if applicable).
OSE	<i>Labeling consult request will be sent as part of DMEP's request.</i>
Pharm/Tox	Review of the genotoxic potential of specified impurities.
QbD	<i>Not applicable</i>

This is a paper NDA, filed as a 505(b)(2) application, with the reference listed drugs (RLD) being (b) (4) Phentermine HCl Capsule (Sandoz), 30 mg and 15 mg. The difference between this new product and the RLDs are the dosage forms.

Note to chemists: the reference to the RLD is for the reliance on FDA's findings of safety and/or effectiveness only, not for any CMC purpose.

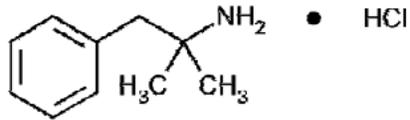
Reference is made to the DMF (b) (4) for the CMC information on the drug substance.

The drug product is an orally disintegrating tablet with 15, 30, (b) (4) mg phentermine HCl. The product will be packaged in 30-count and 100-count bottles. The product is stored at room temperature.

Initial Quality/CMC Assessment
ONDQA

Has all information requested during the IND phases, and at the pre-NDA meetings been included?
Not applicable. No CMC information was requested during the IND phases.

Drug substance:



C₁₀H₁₅N·HCl 185.69

Benzeneethanamine, α , α -dimethyl-, hydrochloride.

α , α -Dimethylphenethylamine hydrochloride

Review comments: Reference is made to the DMF ^{(b) (4)} for all CMC information on the drug substance. This DMF has been reviewed 13 times in support of several other approved applications; it is currently adequate based on the most recent review (10-JUN-2010). The primary reviewer will evaluate any new information in the DMF submitted since the most recent review. The drug substance specification (copied on the next page) is the same as the USP monograph for phentermine HCl, with the addition of Organic Volatile Impurities, Residual Solvents, Assay by HPLC, Solution in ethanol (%transmission, color, clarity), Solution in water (color, clarity), and Impurities. There are 3 specified impurities (copied below). All impurity limits are within the ICH Q3A identification and qualification thresholds.

Impurity Structure	Impurity Formation
(b) (4)	

Initial Quality/CMC Assessment
ONDQA

Table 2.3.S.4.1-1. Phentermine Hydrochloride Drug Substance Specifications.

Phentermine Hydrochloride Drug Substance Specifications		
Test	Method Source	Specification (b) (4)
[Redacted Content]		

Initial Quality/CMC Assessment
ONDQA

Drug product

Table 2.3.P.1-1. Composition of Phentermine HCl ODT Drug Product.

Components	Phentermine HCl 15 mg strength	Phentermine HCl 30 mg strength	(b) (4)
	mg/tablet		
Phentermine HCl	15.00*	30.00*	
Mannitol powder (b) (4)	(b) (4)		
Citric Acid powder			
Povidone CL (b) (4)			
Povidone K 30 (b) (4)			
Sucralose			
Magnesium Stearate			
Peppermint flavour			
Talc			
Sodium Lauryl Sulfate			
Mannitol pregranulated (b) (4)			
FD&C Blue # 1 lake (b) (4)			
FD&C Yellow # 5 lake (b) (4)			

(b) (4)

Components	Reference specifications	Function		
		Phentermine HCl 15 mg ODT	Phentermine HCl 30 mg ODT	Phentermine HCl 37.5 mg ODT
Phentermine HCl	USP	API	API	API
Mannitol powder (b) (4)	EP – USP - NF	(b) (4)		
Citric acid powder	EP – USP - NF			
Povidone CL (b) (4)	EP – USP			
Povidone K 30 (b) (4)	EP – USP			
Sucralose	USP			
Magnesium stearate	EP – NF			
Peppermint flavor	Internal Specification			
Talc	EP – USP - NF			
Sodium lauryl sulfate	EP – USP - NF			
Mannitol pregranulated (b) (4)	EP – USP			
FD&C Blue # 1 lake (b) (4)	FDA			
FD&C Yellow # 5 lake (b) (4)	FDA			

Initial Quality/CMC Assessment
ONDQA

Review comments: (copies of pertinent information are included starting on page 8)

- **Established name and dosage strength.** The established name of the product is “phentermine hydrochloride”, which matches per CDER policy.
- **Comparability of the product used in the clinical studies, stability studies, and commercial product.** Three batches of each dosage strength were manufactured with the commercial process, at production scale, with the commercial formulation. Their manufacture was also part of the manufacturing process validation. Each batch was packaged in the commercial 30-count bottles and 100-count bottles. All batches were placed on stability as primary batches. One batch of each dosage strength in the 100-count bottles was used in the pivotal BE studies: 15-mg batch 034E08, 30-mg batch 036E08. (b) (4)
- **Master batch records** were not included in the initial NDA submission for the commercial manufacturing process (complying with 505(b)(2) regulations). See Comment at the end of this review (sent to Applicant on 25-AUG-2010). In response to FDA’s comment, the applicant submitted the master batch records on 12-OCT-2010 in order to allow the filing of this NDA.
- **Limits on degradation products.** The specified degradants and their proposed limits (b) (4). The limits are below the ICH qualification threshold for the maximum daily dose (b) (4). The applicant should provide a discussion on (b) (4); see the 74-day letter comment at the end of this review. The primary reviewer will evaluate the stability-indicating results of the degradant-determining test method in the validation report.
- **Disintegration.** According the FDA final (December 2008) "Guidance for Industry Orally Disintegrating Tablets", the defining characteristics of this dosage form is the rapid disintegration in saliva without the need for chewing or liquids, and the definition includes an in-vitro disintegration time of approximately 30 seconds or less, when based on the USP disintegration test method or alternative. The stability data in the 11-AUG-2010 NDA submission show disintegration times (b) (4), and the currently drug product specification has a disintegration time of (b) (4). Therefore, (b) (4). See Comment at the end of this review (sent to Applicant on 25-AUG-2010). In response to FDA’s comment, the applicant commits to submitting a revised disintegration test method and supporting data to show that the tablet can meet the revised limit of disintegration in 30 seconds (or less) during the review cycle in order to

Initial Quality/CMC Assessment ONDQA

allow the filing of this NDA. (The applicant states in the 13-OCT-2010 email that the information was submitted on 12-OCT-2010.)

- **Dissolution.** Review of the [REDACTED] ^{(b) (4)} and all dissolution/drug release-related information will be conducted by the ONDQA Biopharm team.
- **Environmental Assessment.** The applicant's claim of categorical exclusion from the requirement to prepare an environmental assessment cites "21 CFR, Part 25, Subpart B, 25.24(c)(4)", which does not exist. See the 74-day letter comment at the end of this review.

Stability:

As mentioned earlier in this review, three batches of each dosage strength were manufactured with the commercial process, at production scale, with the commercial formulation. Each batch was packaged in the commercial 30-count bottles and 100-count bottles. All batches were placed on stability as primary batches. The stability data in the NDA initially included 3-month long-term and accelerated data for two (out of the three) primary batches of each dosage strength, and 24-month long-term and 6-month accelerated data for one primary batch of each dosage strength. See Comment at the end of this review (sent to Applicant on 25-AUG-2010). In response to FDA's comment, the applicant commits to submitting additional 6-month data (on the batches initially submitted with the 3-month data) by November, in order to allow the filing of this NDA (correspondence submitted on 12-OCT-2010.). Each stability batch was packaged in both bottle systems. No photostability study was conducted, and the applicant uses the term "retest period" instead of the correct term "expiration dating period"; see the 74-day letter comments at the end of this review.

Supporting NDA or IND: IND 76477 - same sponsor

Supporting DMFs: See 3.2.P.7 in Volume 4 of the NDA.

GMP facilities: EER was sent to Compliance by ONDQA PM on 31-AUG-2010.

(b) (4)

Initial Quality/CMC Assessment
ONDQA

Scheme 2.3.P.2-1. Manufacturing Process for Phentermine HCl ODT Based Upon Formulation Studies.



(b) (4)

Initial Quality/CMC Assessment
ONDQA

(b) (4)



Initial Quality/CMC Assessment
ONDQA

PRODUCT QUALITY
FILING REVIEW FOR NDA (ONDQA)

NDA Number: 202088

Established/Proper Name:
Phentermine hydrochloride

Applicant: Citius
Pharmaceuticals LLC

Letter Date: 11-AUG-2010

Stamp Date: 17-AUG-2010

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

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			Not applicable. No comment was sent to Sponsor.
B. facilities*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		

Initial Quality/CMC Assessment
ONDQA

8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>	x		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT

Initial Quality/CMC Assessment
ONDQA

	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	x		Incorrect regulation is cited. See Comment at the end of this review.
D. drug substance/active pharmaceutical ingredient (DS/api)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?			Reference is made to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			Reference is made to DMF.
14.	Does the section contain information regarding the characterization of the DS?			Reference is made to DMF.
15.	Does the section contain controls for the DS?			Reference is made to DMF.
16.	Has stability data and analysis been provided for the drug substance?			Reference is made to DMF.
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	
E. drug product (dp)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?		x	Deficiency sent to Applicant on 25-AUG-2010.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?		x	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	

Initial Quality/CMC Assessment
ONDQA

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?		x	See Comment at the end of this review.
G. microbiology				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			
H. master files (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		
I. Labeling				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?		x	Deficiency will be sent by DMEP.
J. filing conclusion				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?			
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	x		See on the last page and the Initial Quality/CMC Assessment.

{See appended electronic signature page}

Su (Suong) Tran
CMC Lead
Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

{See appended electronic signature page}

Ali Al Hakim
Branch Chief
Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

Comments sent on 25-AUG-2010 and resolved during the 01-OCT-2010 teleconference:

- In support of your 505(b)(2) application for an Orally Disintegrating Tablet (ODT) of phentermine hydrochloride, provide a justification for designating your product an ODT.

Initial Quality/CMC Assessment ONDQA

According to the FDA final (December 2008) "Guidance for Industry Orally Disintegrating Tablets", the defining characteristics of this dosage form is the rapid disintegration in saliva without the need for chewing or liquids, and the definition includes an in-vitro disintegration time of approximately 30 seconds or less, when based on the USP disintegration test method or alternative. The stability data in the 11-AUG-2010 NDA submission show disintegration times (b) (4), and your currently drug product specification has a disintegration time of (b) (4).

Applicant's response: The designation "ODT" will apply to this product based on a revised analytical method that would have FDA's 30-second disintegration threshold (see 12-OCT-2010 amendment).

- As required by 21 CFR 314.54 (i.e., for a 505(b)(2) application), submit the proposed or actual master production record of the commercial drug product. As required by 21 CFR 314.50, submit the executed batch records for each batch of the drug product used to conduct the pivotal bioavailability or bioequivalence study.

Applicant's response: One copy of the master batch records will be submitted (see 12-OCT-2010 amendment).

- The ICH final (November 2003) Guidance Q1A(R2) Stability Testing of New Drug Substances and Products states "The long-term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission". The primary drug product stability data in the 11-AUG-2010 NDA submission include 3-month long-term data for two (out of the three) primary batches of each dosage strength. Provide a justification for your request to file the NDA with such limited stability data.

Applicant's response: Additional 6-month accelerated and long-term stability data will be submitted by November.

- The following issue was identified as a review issue for CMC but as a filing deficiency for the PharmTox team. It was conveyed to the applicant during the 01-OCT-2010 teleconference: (b) (4)

Applicant's response: The applicant indicated that some information was submitted in the NDA but may be difficult for FDA to find. Additional information was submitted on 12-OCT-2010 to allow a filing recommendation from the PharmTox team.

74-Day Letter – Draft Comments to the Applicant:

Note to Reviewers: The following comments to the Applicant **do not include all the critical issues discussed in this IQA/filing review**. Issues discussed in this IQA/filing review are for the primary reviewer's consideration and may not necessarily be included in the 74-day letter.

The applicant's response to the 74-day letter comments will be documented and evaluated as part of the primary CMC review.

Initial Quality/CMC Assessment
ONDQA

1. Your claim of categorical exclusion from the requirement to prepare an environmental assessment cites “21 CFR, Part 25, Subpart B, 25.24(c)(4)”, which does not exist. Submit a revised claim with the correct regulation citation, information to support the requested exclusion (e.g., a calculation of estimated environmental concentrations of the drug), and a statement that, to the best of your knowledge, no extraordinary circumstance exists that would warrant the preparation of an environmental assessment.
2. Provide the location in the NDA of the photostability study report for the drug product.
3. The term “retest period” does not apply to the drug product. Revise your NDA where appropriate to replace “retest period” with the correct term “expiration dating period” when discussing the drug product.

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

/s/

SUONG T TRAN
10/14/2010

ALI H AL HAKIM
10/14/2010