

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-418

CHEMISTRY REVIEW(S)

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

Application:	NDA 22418/000	Sponsor:	MUTUAL PHARM
Code:	510		1400 SOUTH ORANGE AVE
Y:	5S		ORLANDO, FL 32806
Stamp Date:	15-AUG-2008	Brand Name:	FENOFIBRIC ACID TABS 35MG/105MG ORAL
PDUFA Date:	15-JUN-2009	Estab. Name:	
Action Goal:		Generic Name:	FENOFIBRIC ACID TABS 35MG/105MG ORAL
District Goal:	16-APR-2009	Dosage Form:	(TABLET)
		Strength:	35 MG, 105 MG
FDA Contacts:	K. JOHNSON	Project Manager	301-796-1234
	Y. YANG	Review Chemist	301-796-1777
	S. TRAN	Team Leader	301-796-1784

Overall Recommendation: ACCEPTABLE on 11-JUN-2009 by E. JOHNSON (HFD-320) 301-796-3334

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

DMF No: _____ **AADA:** _____

Responsibilities: FINISHED DOSAGE RELEASE TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-SEP-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

DMF No: _____ **AADA:** _____

Responsibilities: FINISHED DOSAGE RELEASE TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-SEP-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

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

DMF No: _____ AADA: _____
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: _____ OAI Status: NONE b(4)
Last Milestone: OC RECOMMENDATION
Milestone Date: 11-JUN-2009
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

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

DMF No: _____ AADA: _____
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 10-SEP-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

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

DMF No: _____ AADA: _____
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 10-SEP-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

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

Establishment: CFN: 2523348 FEI: 2523348
MUTUAL PHARMACEUTICAL COMPANY, INC.
1100 ORTHODOX ST
PHILADELPHIA, PA 19124

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE MANUFACTURER
Profile: TABLETS, PROMPT RELEASE OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 11-DEC-2008
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: [REDACTED] FEI: [REDACTED] b(4)

DMF No: AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Milestone: OC RECOMMENDATION
Milestone Date: 10-SEP-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: [REDACTED] FEI: [REDACTED] b(4)

DMF No: AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 10-SEP-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

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

Establishment: CFN: _____ FEI: _____ b(4)
[] []

DMF No: _____ **AADA:** b(4)

Responsibilities: FINISHED DOSAGE RELEASE TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-SEP-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: _____ FEI: _____ b(4)
[] []

DMF No: _____ **AADA:** _____

Responsibilities: FINISHED DOSAGE RELEASE TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-SEP-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: _____ FEI: _____ b(4)
[] []

DMF No: _____ **AADA:** _____

Responsibilities: FINISHED DOSAGE RELEASE TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-SEP-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

/s/

NICKEISHA S BURFORD
09/18/2009

6/15/09

NDA 22-418

Fibricor™ (Fenofibric Acid) Tablets

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

Applicant: Mutual Pharmaceutical Company, Inc.
1100 Orthodox Street
Philadelphia, PA 19124

Indication: -Treatment of hypercholesterolemia (recommended initial dose 105 mg), specifically as adjunctive therapy to diet to reduce elevated low density lipoprotein cholesterol (LDL-C), total cholesterol (Total-C), triglycerides, and apolipoprotein B (apo B), and to increase high density lipoprotein cholesterol (HDL-C) in adult patients with primary hypercholesterolemia or mixed dyslipidemia.
-Treatment of hypertriglyceridemia (recommended initial dose 35 mg - 105 mg), specifically as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia.

Presentation: The drug product tablet is manufactured in two strengths, 35 mg and 105 mg immediate release tablets. The tablets are packaged in _____ bottles _____

containing 30 to 1000 tablets per bottle together with _____

_____ The lower tablet-count bottle configurations for the 35-mg tablets are the _____ bottles containing 30 or 60 tablets and the _____ bottles containing 90 tablets. The lower tablet-count bottle configurations for the 105-mg tablets are the _____ bottles containing 30 tablets, the _____ bottles containing 60 tablets, and the _____ bottles containing 90 tablets. Bottles are equipped with _____

b(4)

b(4)

b(4)

EER Status:	Recommendation:	Acceptable
Consults:	EA -	Categorical exclusion provided
	CDRH-	N/A
	Statistics -	N/A
	Methods Validation -	Not recommended
	Clinical Pharmacology-	N/A
	Microbiology -	N/A
	Pharm/toxicology -	Acceptable

Original Submission: 15-August-2008

Re-submissions: N/A

Post-Approval CMC Agreements: None beyond the typical stability commitments.

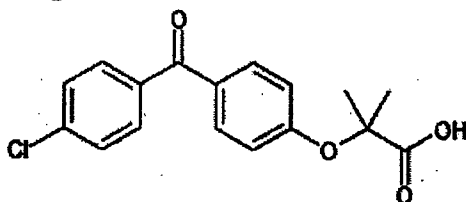
Background:

This is a 505(b)(2) application based on the approved NDA 21-656 TriCor (fenofibrate) Tablets. The drug substance, fenofibric acid, is the active ingredient. The drug product is a single-entity, immediate-release tablet available in two strengths: 35 mg and 105 mg fenofibric acid.

Summary

Drug Substance:

Fenofibric acid, chemical name 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoic acid, molecular formula $C_{17}H_{15}ClO_4$ and molecular weight 318.75 g/mol.



Fenofibric acid drug substance is manufactured and supplied to Mutual (NDA applicant) by _____ b(4)

Chemistry, manufacture and controls information (CMC) for fenofibric acid drug substance is described in _____ s Type I DMF _____ DMF _____ has been reviewed and found acceptable. b(4)

Fenofibric acid drug substance employed for the manufacture of Fenofibric Acid Tablets are tested for appearance, identified by HPLC (retention time) and UV, melting point (mp 179 - 183 °C), water content (NMT _____), chloride content (NMT _____), sulfate content (NMT _____), residue on ignition _____ b(4)

fenofibric acid content / _____, %, calculated or _____ (basis), residual solvents / _____ NMT _____, and _____ NMT _____ b(4)

and particle size distribution. Known impurities such as _____ and _____ are NMT _____ each. Any unspecified impurity can not exceed _____ and the total amount NMT _____

The drug substance is stored the same container closure as received from _____ b(4)

_____ at a temperature below 30 °C.

The proposed re-test period is of _____ for the bulk drug substance. This is supported by the available stability data provided in DMF _____ b(4)

Conclusion: The drug substance is satisfactory.

Drug Product:

Fibricor™ Tablets are immediate release tablets manufactured from a common blend using different blend weights and tablet sizes/thicknesses to produce the desired strengths. The manufacturing process is a _____

b(4)

_____ Tablet strength are differentiated by size, shape and debossing.

The tablet strengths are dose proportional; the blend w/w composition corresponds to _____ Fenofibric Acid (active component) _____ of _____ microcrystalline Cellulose _____ Copovidone _____ used as _____ (w/w) Crospovidone _____, employed as a _____ and _____ (w/w) of the _____ Magnesium Stearate. All excipients meet compendial requirements. The total weight of the 35 mg and 105 mg tablets are _____ and _____, respectively.

b(4)

Fibricor™ Tablets specifications include Appearance (visual), Identification by both HPLC and UV, Water Content _____, Assay by HPLC (_____ %), Dissolution (Q _____ in 15 minutes; 900 ml media pH 6.8, USP Apparatus 2 (paddle), and 75 rpm), Content Uniformity (USP <905>), and Purity. The amount of the known impurities _____ and _____ cannot exceed _____ each, any unspecified impurity content NMT _____, and the total Related Substances/Degradation Products can not exceed _____

b(4)

b(4)

b(4)

The proposed expiry date of 24 months for the drug product, when stored at the recommended condition (Store at 20 ° to 25 °C (68 ° to 77 °F) [See USP Controlled Room Temperature]; dispense in tight, light-resistant container"), is fully supported by the available stability data.

Conclusion: The drug product is satisfactory.

Overall Conclusion: From Chemistry, Manufacturing and Control perspective, the application is recommended for approval.

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

1 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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

/s/

Ali Al-Hakim
6/15/2009 05:39:58 PM
CHEMIST

6/12/09

NDA 22-418

**Fibricor™
(Fenofibric Acid) Tablets**

Mutual Pharmaceutical Company, Inc.

**Yvonne Yang, Ph.D.
Xavier Ysern, Ph.D.**

Office of New Drug Quality Assessment

Division of Metabolism and Endocrinology Products

CHEMISTRY REVIEW

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet	3
The Executive Summary	6
I. Recommendations	6
A. Recommendation and Conclusion on Approvability	6
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	6
II. Summary of Chemistry Assessments	6
A. Description of the Drug Product(s) and Drug Substance(s)	6
B. Description of How the Drug Product is Intended to be Used	8
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
Amendmant dated 29-May-2009	9
III. List of Deficiencies To Be Communicated (None)	
Attached	13

CHEMISTRY REVIEW

Chemistry Review Data Sheet

1. NDA 22-418
2. REVIEW #: # 2
3. REVIEW DATE: 12-Jun-2009
4. REVIEWER(S): Yvonne Yang, Ph.D., and Xavier Ysern, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

N/A

Document Date

--

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Amendment 0009 (response to Agency's CMC request dated 09-May-2009)

Document Date

29-May-2009

Previously reviewed:

Original submission

15-Aug-2008

Amendment 0001 (CMC stability replacement file for original NDA)

18-Sept-2008

Amendment 0002 (stability data update, _____, draft labeling with proposed Tradename Fibracor™)

30-Sept-2008

Amendment 0003 (Request for Proprietary Name review: Fibracor™, _____)

10-Oct-2008

Amendment 0004 (response to FDA filing communication: chemistry and clinical pharmacology)

14-Nov-2008

Amendment 0007 (stability data update)

15-Jan-2009

Amendment 0008 (dissolution data in multiple media, stability data update)

04-Mar-2009

b(4)

b(4)

7. NAME & ADDRESS OF APPLICANT:

Name: Mutual Pharmaceutical Company, Inc.

Address: 1100 Orthodox Street
Philadelphia, PA 19124

Representative: Robert Dettery
Vice President, Regulatory Affairs

Telephone: 215-288-6500

8. DRUG PRODUCT NAME/CODE/TYPE:

- | | |
|--|----------------------------------|
| • Proprietary Name: | Fibracor™ |
| • Non-Proprietary Name (USAN): | Fenofibric acid |
| • Code Name/# (ONDQA only): | CAS-42017-89-0 (fenofibric acid) |
| • Chem. Type/Submission Priority (ONDQA only): | |
| • Chem. Type: | S |
| • Submission Priority: | S |

CHEMISTRY REVIEW

B. Other Documents:

Document	Application #	Description
NDA IND	21-656 (Abbott Laboratories) 76,749 (Mutual Pharmaceutical Company, Inc.)	Reference listed product TriCor (fenofibrate) Tablets 48 mg and 145 mg Adjunctive therapy to diet to reduce elevated LDP, total cholesterol, triglycerides and Apoprotein B and increase HDL

18. STATUS:

Consults	Recommendation	Date	Reviewer
EES	Acceptable (District Office recommendation)	11-Jun-2009	
Biometrics	--		
Labeling	Acceptable	29-May-2009	
Biopharmaceutics (ONDQA Team)	Dissolution specification accepted on interim basis _____ will be requested.	13-May-2009	Houda Mahayni, PhD
Pharm/Tox	--		
DMEPA	No objection to the proposed proprietary name Fibracor™	07-May-2009	Robin Duer, RN, MBA
EA	Environment Assessment (EA) Categorical exclusion granted	N/A	Part of this review
Methods Validation	Revalidation by Agency Laboratories not recommended	N/A	Part of this review
Microbiology	N/A	N/A	

b(4)

CHEMISTRY REVIEW

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view this application is recommended for approval. All pending issues have been resolved.

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

The proposed dissolution specification is acceptable

b(4)

(This request has been accepted by the applicant, Mutual, on amendment dated 29 May 2009.)

II. Summary of Chemistry Assessments

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

Fenofibric acid is the active moiety of fenofibrate, a lipid-lowering drug first approved by the Agency in 1993. Fenofibrate is currently available in a number of tablet and capsule formulations. Since the parent drug (fenofibrate) is not present in plasma, the pharmacokinetic as well as pharmacodynamic properties of fenofibrate drug products are characterized by fenofibric acid levels and the pharmacological response to this active metabolite. TriCor® (Fenofibrate) Tablets (Abbott Laboratories' drug product, NDA 21656 approved on November 6, 2004) is the chosen reference listed drug (RLD) for the purpose of this NDA. These new TriCor 145 mg and 48 mg tablets replaced and offer the same effectiveness at lower dosage strength than the previous 160 mg and 54 mg tablets, but now can be taken with or without food. The 35 mg and 105 mg Fenofibric tablets proposed in this NDA are described as bioequivalent to the reference listed drug TriCor 48 mg and 145 mg tablets, respectively. Bioequivalence studies that Fibracor 105 mg tablets are equivalent to TriCor 145 mg tablets, and that Fibracor 105 mg tablets are equivalent to three (3) 35 mg Fibracor tablets.

• Drug Substance

Fenofibric acid, chemical name 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoic acid, molecular formula $C_{17}H_{13}ClO_4$ and molecular weight 318.75 g/mol, is the drug substance of the drug product Fenofibric Acid Tablets. Fenofibric acid is the active component of the pro-drug ester compound fenofibrate. Both fenofibric acid and fenofibrate are drug substances of approved drug products of the fibrate class. As other fibrates, fenofibric acid and fenofibrate are mainly used to reduce both low-density lipoprotein (LDL) and very low density lipoprotein (VLDL) levels, as well as to increase high-density lipoprotein (HDL). The physiological effects of fenofibric acid have been attributed to the activation of peroxisome proliferator activated receptor α (PPAR α). Fenofibric acid is a Biopharmaceutics Classification System (BCS) Class 2 drug. Whereas, the drug is highly soluble in aqueous media of pH ≥ 6.5 , it is not highly soluble across the pH range of 1 to 7.5. The drug is highly permeable based on an *in vitro* model, Caco-2 cells (further confirmed by the estimated 100 % bioavailability).

b(4)

Fenofibric acid drug substance is manufactured and supplied to Mutual (NDA applicant) by _____ Chemistry manufacture and controls information (CMC) for fenofibric acid drug substance is described under _____, Type — DMF — DMF — is been reviewed and found acceptable for its use in the manufacture of Fenofibric Acid Tablets. As DM — is proprietary information, only information on the drug substance provided in the NDA submission will be given below.

b(4)

The drug substance is a white to almost white crystalline powder. Its aqueous solubility increases with pH water (0.1 – 1.7 mg/mL). Log $P_{octanol/water} = 3.585$ (the value for fenofibrate is 5.57) _____ have been described for fenofibric acid, _____ and _____ drug substance was found to match the reference standard of _____

b(4)

CHEMISTRY REVIEW

Fenofibric acid drug substance employed for the manufacture of Fenofibric Acid Tablets are tested for appearance, identified by HPLC (retention time) and UV, melting point (mp 179 – 183 °C), water content _____, chloride content _____, sulfate content (NMT _____), residue on ignition (_____%), fenofibric acid content _____, calculated on _____ basis), purity, residual solvents _____ NMT _____ and _____ NMT _____ and particle size distribution. Known impurities such as _____ and _____ are NMT _____ each. Any unspecified impurity can not exceed _____ and the total amount NMT _____.

b(4)

Mutual stores the drug substance in the same container closure as received from _____ at a temperature below 30 °C.

b(4)

The proposed re-test period of _____ for the bulk drug substance from _____, when stored at 25 °C/ 60 % RH, is supported by the available stability data provided in DMF _____.

b(4)

Drug Product

The drug product Fibracor™ (fenofibric acid) Tablets is manufactured in two strengths, 35 mg and 105 mg immediate release tablets. The proposed 35 mg tablet is described as white, round, debossed 'AR 787' on one side and blank on the other side. The 105 mg tablet is described as white, modified oval, debossed 'AR 788' on one side and blank on the other side.

The tablet strengths are dose proportional, manufactured from a common blend. The blend w/w composition corresponds to _____ Fenofibric Acid (active component), _____ microcrystalline Cellulose _____ Copovidone _____ used as a _____ (w/w) Croscopovidone _____ employed as a _____, and _____ (w/w) of the _____ Magnesium Stearate. All excipients meet compendial requirements. The total weight of the 35 mg and 105 mg tablets are _____ and _____ respectively.

b(4)

Fibracor™ Tablets are manufactured from a common blend using different blend weights and tablet sizes/thicknesses to produce the desired strengths. The manufacturing process is conventional for tablets. _____ Process operations include: (1) _____.

b(4)

Tablet strength are differentiated by size, shape and debossing.

Three registration batches of each strength of drug product were manufactured by Mutual in June-July 2007 under current Good Manufacturing Practices at a pilot scale of _____ tablets (35 mg/105 mg). One batch of each strength, Batch BB 787 0307 (35 mg) and batch BB 788 0318 (105 mg), was used in the pharmacokinetic and/or clinical pharmacology studies in support of the NDA. Commercial manufacture scale of _____ tablets (35 mg/105 mg) is approximately _____ pilot scale.

b(4)

The tablets are packaged in _____ bottles _____ containing 30 to 1000 tablets per bottle together with a _____. The lower tablet-count bottle configurations for the 35-mg tablets are the _____ bottles containing 30 or 60 tablets and the _____ bottles containing 90 tablets. The lower tablet-count bottle configurations for the 105-mg tablets are the _____ bottles containing 30 tablets, the _____ bottles containing 60 tablets, and the _____ bottles containing 90 tablets. All these bottles are equipped with _____.

b(4)

Fibracor™ Tablets specifications include Appearance (visual), Identification by both HPLC and UV, Water Content _____, Assay by HPLC _____, Dissolution (Q= _____ in 15 minutes; 900 ml media pH 6.8, USP Apparatus 2 (raddle), and 75 rpm), Content Uniformity (USP <905>), and Purity. The amount of the known impurities _____ and _____ cannot exceed _____ each, any unspecified impurity content NMT _____, and the total Related Substances/Degradation Products can not exceed _____.

b(4)

CHEMISTRY REVIEW

The stability studies include primary (6 batches: 3 batches 35 mg and 3 batches 105 mg) and supportive (4 batches: one for 30 mg, 50 mg, 90 mg and 130 mg strengths) stability data. 6 months of stability data under accelerated conditions ($40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \pm 5\% \text{RH}$) are provided for both primary and supportive stability data (completed studies). The primary stability study, which still is an ongoing study under long term conditions ($25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 5\% \text{RH}$), includes stability data up to 18 months for the 35 mg strength, and up to 12 months for 105 mg strength. The supportive data under long term conditions, which include bracketing data for non-commercial strengths, includes 18 months stability data for the 30 mg and 24 months for the 50 mg, 90 mg and 130 mg. The stability results indicate that for all evaluated conditions the test results do not differ appreciable from the initial (release) values.

The proposed expiry date of 24 months for the drug product, when stored at the recommended condition (Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]; dispense in tight, light-resistant container"), is fully supported by the available stability data.

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

FibricorTM (fenofibric acid) tablets are intended to be administered orally without regard to meals. As indicated in the package insert, patients should be placed on an appropriate lipid-lowering diet before receiving fenofibric acid, and should continue this diet during treatment with fenofibric acid. The proposed indications for Mutual's fenofibric acid tablets are identical to those currently approved for fenofibrate and include:

- Treatment of hypercholesterolemia (recommended initial dose 105 mg), specifically as adjunctive therapy to diet to reduce elevated low density lipoprotein cholesterol (LDL-C), total cholesterol (Total-C), triglycerides, and apolipoprotein B (apo B), and to increase high density lipoprotein cholesterol (HDL-C) in adult patients with primary hypercholesterolemia or mixed dyslipidemia; and
- Treatment of hypertriglyceridemia (recommended initial dose 35 mg – 105 mg), specifically as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia.

C. Basis for Approvability or Not-Approval Recommendation

NDA 22-224 is recommended for Approval from the standpoint of chemistry, manufacturing and controls (CMC).

III. Administrative

A. Reviewer's Signature

Xavier Ysern, PhD Review Chemist/ ONDQA/ DPAI/ Branch II

B. Endorsement Block

Ali Al-Hakim, PhD Branch Chief/ ONDQA/ DPAI/ Branch II

B. CC Block

Kati Johnson Project Manager/ OND/ ODE II/ DMEP

3 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

C. Establishment of Inspection *Satisfactory*

All facilities involved in the quality (manufacture, testing, and packaging) have found acceptable. An acceptable overall recommendation was issued on June 11, 2009, by the District Office (EER summary report dated 12-Jun-2009 is attached).

ATTACHED:

EER Summary Report dated 12-Jun-2009 (4 pages)

Page
13

CHEMISTRY REVIEW

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 22416/000	Sponsor:	MUTUAL PHARM
Org. Code:	510		1400 SOUTH ORANGE AVE
Priority:	05		ORLANDO, FL 32806
Stamp Date:	15-AUG-2008	Brand Name:	FENOFIBRIC ACID TABS 35MG/100MG ORAL
PDUSA Date:	15-JUN-2008	Batch Name:	
Action Code:		Generic Name:	FENOFIBRIC ACID TABS 35MG/100MG ORAL
District Code:	16-APR-2008	Dosage Form:	(TABLET)
		Strength:	35 MG, 100 MG

FDA Contacts:	K. JOHNSON	Project Manager	301-795-1234
	Y. YANG	Review Chemist	301-795-1777
	B. TRAN	Team Leader	301-795-1764

Overall Recommendation: ACCEPTABLE on 11-JUN-2008 by E. JOHNSON (HFD-320) 301-795-3334

Establishment: CMC: FIC: b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: QC RECOMMENDATION

Milestone Date: 10-SEP-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CMC: FIC: b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: QC RECOMMENDATION

Milestone Date: 10-SEP-2008

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

June 12, 2008 5:00 AM

FDA Confidential - Internal Distribution Only

Page 1 of 4

CHEMISTRY REVIEW

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Establishment:	CFR: _____	FE: _____	b(4)
DMF No:		ANDA:	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:		ONI Status:	NONE b(4)
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	11-JUN-2008		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		
Establishment:	CFR: _____	FE: _____	b(4)
DMF No:		ANDA:	
Responsibilities:	FINISHED DOSEAGE RELEASE TESTER		
Profile:	CONTROL TESTING LABORATORY		ONI Status: NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	10-SEP-2008		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		
Establishment:	CFR: _____	FE: _____	b(4)
DMF No:		ANDA:	
Responsibilities:	FINISHED DOSEAGE RELEASE TESTER		
Profile:	CONTROL TESTING LABORATORY		ONI Status: NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	10-SEP-2008		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

CHEMISTRY REVIEW

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Establishment: CFE: _____ FRI: _____ b(4)
 []
DMF No: _____ **ANDA:** _____
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY **QM Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 18-SEP-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFE: _____ FRI: _____ b(4)
 []
DMF No: _____ **ANDA:** _____
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY **QM Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 19-SEP-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFE: _____ FRI: _____ b(4)
 []
DMF No: _____ **ANDA:** _____
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY **QM Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 19-SEP-2008
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

CHEMISTRY REVIEW

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Establishment: CFE: 2023348 FBR: 2023348
MUTUAL PHARMACEUTICAL COMPANY, INC.
1100 ORTHODOX ST
PHILADELPHIA, PA 19134

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE MANUFACTURER
Profile: TABLETS, PROMPT RELEASE ON Status: NONE
Last Milestone: QC RECOMMENDATION
Milestone Date: 11-DEC-2004
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFE: FBR: b(4)

DMF No: AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY ON Status: NONE
Last Milestone: QC RECOMMENDATION
Milestone Date: 10-SEP-2003
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFE: FBR: b(4)

DMF No: AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY ON Status: NONE
Last Milestone: QC RECOMMENDATION
Milestone Date: 10-SEP-2003
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

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

/s/

Xavier Ysern
6/12/2009 08:53:06 AM
CHEMIST

Ali Al-Hakim
6/12/2009 11:18:36 AM
CHEMIST

5/18/09

CHEMISTRY REVIEW

NDA 22-418

**Fibricor™
(Fenofibric Acid) Tablets**

Mutual Pharmaceutical Company, Inc.

**Yvonne Yang, Ph.D.
Xavier Ysern, Ph.D.**

Office of New Drug Quality Assessment

Division of Metabolism and Endocrinology Products



CHEMISTRY REVIEW



Table of Contents

Table of Contents	2
Chemistry Review Data Sheet	3
The Executive Summary	6
I. Recommendations	6
A. Recommendation and Conclusion on Approvability	6
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	6
II. Summary of Chemistry Assessments	6
A. Description of the Drug Product(s) and Drug Substance(s)	6
B. Description of How the Drug Product is Intended to be Used	8
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 Fenofibric Acid	9
P DRUG PRODUCT Fibracor™ (fenofibric acid) Tablets	20
A APPENDICES	56
R REGIONAL INFORMATION	56
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	57
A. Labeling & Package Insert	58
B. Environmental Assessment or Claim of Categorical Exclusion	59
C. Establishment of Inspection	60
III. List of Deficiencies To Be Communicated	60
Attached	61



CHEMISTRY REVIEW



Chemistry Review Data Sheet

1. NDA 22-418
2. REVIEW #: # 1
3. REVIEW DATE: 12-May-2009
4. REVIEWER(S): Yvonne Yang, Ph.D., and Xavier Ysern, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

N/A

Document Date

-

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original submission

15-Aug-2008

Amendment 0001 (CMC stability replacement file for original NDA)

18-Sept-2008

Amendment 0002 (stability data update, draft labeling with proposed Tradename Fibracor™)

30-Sept-2008

b(4)

Amendment 0003 (Request for Proprietary Name review: Fibracor™)

10-Oct-2008

b(4)

Amendment 0004 (response to FDA filing communication: chemistry and clinical pharmacology)

14-Nov-2008

Amendment 0007 (stability data update)

15-Jan-2009

Amendment 0008 (dissolution data in multiple media, stability data update)

04-Mar-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Mutual Pharmaceutical Company, Inc.

Address: 1100 Orthodox Street
Philadelphia, PA 19124

Representative: Robert Dettery
Vice President, Regulatory Affairs

Telephone: 215-288-6500

8. DRUG PRODUCT NAME/CODE/TYPE:

- Proprietary Name: Fibracor™
- Non-Proprietary Name (USAN): Fenofibric acid
- Code Name/# (ONDQA only): CAS-42017-89-0 (fenofibric acid)
- Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: S
 - Submission Priority: S



CHEMISTRY REVIEW



B. Other Documents:

Document	Application #	Description
NDA IND	21-656 (Abbott Laboratories) 76,749 (Mutual Pharmaceutical Company, Inc.)	Reference listed product TriCor (fenofibrate) Tablets 48 mg and 145 mg Adjunctive therapy to diet to reduce elevated LDP, total cholesterol, triglycerides and Apoprotein B and increase HDL

18. STATUS:

Consults	Recommendation	Date	Reviewer
EES	Pending		
Biometrics	--		
Labeling	Labeling issues still under review (multi disciplinary approach)		
Biopharmaceutics (ONDQA Team)	Dissolution specification accepted on interim basis	13-May-2009	Houda Mahayni, PhD
Pharm/Tox	--		
DMEPA	No objection to the proposed proprietary name Fibracor™	07-May-2009	Robin Duer, RN, MBA
EA	Environment Assessment (EA) Categorical exclusion granted	N/A	Part of this review
Methods Validation	Revalidation by Agency Laboratories not recommended	N/A	Part of this review
Microbiology	N/A	N/A	

b(4)



CHEMISTRY REVIEW



The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view this application is recommended for approval pending an acceptable recommendation for the overall cGMP status by the Office of Compliance, satisfactory resolution of the Agency requests listed under "List of Deficiencies to be Communicated", and final labeling.

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

The proposed dissolution specification is acceptable

b(4)

II. Summary of Chemistry Assessments

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

Fenofibric acid is the active moiety of fenofibrate, a lipid-lowering drug first approved by the Agency in 1993. Fenofibrate is currently available in a number of tablet and capsule formulations. Since the parent drug (fenofibrate) is not present in plasma, the pharmacokinetic as well as pharmacodynamic properties of fenofibrate drug products are characterized by fenofibric acid levels and the pharmacological response to this active metabolite. TriCor® (Fenofibrate) Tablets (Abbott Laboratories' drug product, NDA 21656 approved on November 6, 2004) is the chosen reference listed drug (RLD) for the purpose of this NDA. These new TriCor 145 mg and 48 mg tablets replaced and offer the same effectiveness at lower dosage strength than the previous 160 mg and 54 mg tablets, but now can be taken with or without food. The 35 mg and 105 mg Fenofibric tablets proposed in this NDA are described as bioequivalent to the reference listed drug Tricor 48 mg and 145 mg tablets, respectively. Bioequivalence studies that Fibracor 105 mg tablets are equivalent to Tricor 145 mg tablets, and that Fibracor 105 mg tablets are equivalent to three (3) 35 mg Fibracor tablets.

Drug Substance

Fenofibric acid, chemical name 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoic acid, molecular formula $C_{17}H_{15}ClO_4$, and molecular weight 318.75 g/mol, is the drug substance of the drug product Fenofibric Acid Tablets. Fenofibric acid is the active component of the pro-drug ester compound fenofibrate. Both fenofibric acid and fenofibrate are drug substances of approved drug products of the fibrate class. As other fibrates, fenofibric acid and fenofibrate are mainly used to reduce both low-density lipoprotein (LDL) and very low density lipoprotein (VLDL) levels, as well as to increase high-density lipoprotein (HDL). The physiological effects of fenofibric acid have been attributed to the activation of peroxisome proliferator activated receptor α (PPAR α). Fenofibric acid is a Biopharmaceutics Classification System (BCS) Class 2 drug. Whereas, the drug is highly soluble in aqueous media of pH $\geq$ 6.5, it is not highly soluble across the pH range of 1 to 7.5. The drug is highly permeable based on an *in vitro* model, Caco-2 cells (further confirmed by the estimated 100 % bioavailability).

Fenofibric acid drug substance is manufactured and supplied to Mutual (NDA applicant) by _____ Chemistry. manufacture and controls information (CMC) for fenofibric acid drug substance is described under _____, Type ~~DMF~~ _____ DMF _____ has been reviewed and found acceptable for its use in the manufacture of Fenofibric Acid Tablets. As DMF _____ is proprietary information, only information on the drug substance provided in the NDA submission will be given below.

b(4)

b(4)

The drug substance is a white to almost white crystalline powder. Its aqueous solubility increases with pH water (0.1 – 1.7 mg/mL). Log $P_{octanol/water}$ = 3.585 (the value for fenofibrate is 5.57). _____ have been described for fenofibric acid, _____ and _____ drug substance was found to match the reference standard of _____

b(4)



CHEMISTRY REVIEW



Fenofibric acid drug substance employed for the manufacture of Fenofibric Acid Tablets are tested for appearance, identified by HPLC (retention time) and UV, melting point (mp 179 – 183 °C), water content, chloride content, sulfate content, residue on ignition, fenofibric acid content, calculated on basis, purity, residual solvents, NMT, and NMT, and particle size distribution. Known impurities such as and are NMT each. Any unspecified impurity can not exceed, and the total amount NMT.

b(4)

b(4)

Mutual stores the drug substance in the same container closure as received from at a temperature below 30 °C.

b(4)

The proposed re-test period of for the bulk drug substance from when stored at 25 °C/ 60 % RH, is supported by the available stability data provided in DMF.

b(4)

Drug Product

The drug product Fibracor™ (fenofibric acid) Tablets is manufactured in two strengths, 35 mg and 105 mg immediate release tablets. The proposed 35 mg tablet is described as white, round, debossed 'AR 787' on one side and blank on the other side. The 105 mg tablet is described as white, modified oval, debossed 'AR 788' on one side and blank on the other side.

The tablet strengths are dose proportional, manufactured from a common blend. The blend w/w composition corresponds to Fenofibric Acid (active component), of microcrystalline Cellulose, Copovidone, used as a (w/w) Croscopvidone employed as a, and (w/w) of the, Magnesium Stearate. All excipients meet compendial requirements. The total weight of the 35 mg and 105 mg tablets are, and respectively.

b(4)

b(4)

Fibracor™ Tablets are manufactured from a common blend using different blend weights and tablet sizes/thicknesses to produce the desired strengths. The manufacturing process is conventional for tablets. Process operations include:

b(4)

Tablet strength are differentiated by size, shape and debossing.

Three registration batches of each strength of drug product were manufactured by Mutual in June-July 2007 under current Good Manufacturing Practices at a pilot scale of tablets (35 mg/105 mg). One batch of each strength, Batch BB 787 0307 (35 mg) and batch BB 788 0318 (105 mg), was used in the pharmacokinetic and/or clinical pharmacology studies in support of the NDA. Commercial manufacture scale of tablets (35 mg/105 mg) is approximate pilot scale.

b(4)

b(4)

The tablets are packaged in containing 30 to 1000 tablets per bottle together with a. The lower tablet-count bottle configurations for the 35-mg tablets are the bottles containing 30 or 60 tablets and the bottles containing 90 tablets. The lower tablet-count bottle configurations for the 105-mg tablets are the bottles containing 30 tablets, the bottles containing 60 tablets and the bottles containing 90 tablets. All these bottles are equipped with.

b(4)

Fibracor™ Tablets specifications include Appearance (visual), Identification by both HPLC and UV, Water Content (NMT), Assay by HPLC, Dissolution (Q= in 15 minutes; 900 ml media pH 6.8, USP Apparatus 2 (paddle), and 75 rpm), Content Uniformity (USP <905>), and Purity. The amount of the known impurities and cannot exceed, each, any unspecified impurity content NMT, and the total Related Substances/Degradation Products can not exceed.

b(4)

b(4)



CHEMISTRY REVIEW



The stability studies include primary (6 batches: 3 batches 35 mg and 3 batches 105 mg) and supportive (4 batches: one for 30 mg, 50 mg, 90 mg and 130 mg strengths) stability data. 6 months of stability data under accelerated conditions ($40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \pm 5\% \text{RH}$) are provided for both primary and supportive stability data (completed studies). The primary stability study, which still is an ongoing study under long term conditions ($25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 5\% \text{RH}$), includes stability data up to 18 months for the 35 mg strength, and up to 12 months for 105 mg strength. The supportive data under long term conditions, which include bracketing data for non-commercial strengths, includes 18 months stability data for the 30 mg and 24 months for the 50 mg, 90 mg and 130 mg. The stability results indicate that for all evaluated conditions the test results do not differ appreciable from the initial (release) values.

The proposed expiry date of 24 months for the drug product, when stored at the recommended condition (Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]; dispense in tight, light-resistant container”), is fully supported by the available stability data.

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

Fibricor™ (fenofibric acid) tablets are intended to be administered orally without regard to meals. As indicated in the package insert, patients should be placed on an appropriate lipid-lowering diet before receiving fenofibric acid, and should continue this diet during treatment with fenofibric acid. The proposed indications for Mutual's fenofibric acid tablets are identical to those currently approved for fenofibrate and include:

- Treatment of hypercholesterolemia (recommended initial dose 105 mg), specifically as adjunctive therapy to diet to reduce elevated low density lipoprotein cholesterol (LDL-C), total cholesterol (Total-C), triglycerides, and apolipoprotein B (apo B), and to increase high density lipoprotein cholesterol (HDL-C) in adult patients with primary hypercholesterolemia or mixed dyslipidemia; and
- Treatment of hypertriglyceridemia (recommended initial dose 35 mg – 105 mg), specifically as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia.

C. Basis for Approvability or Not-Approval Recommendation

NDA 22-224 is recommended for Approval from the standpoint of chemistry, manufacturing and controls (CMC) pending: (1) an acceptable recommendation for the overall cGMP status by the Office of Compliance, (2) satisfactory resolution of the Agency requests listed under “List of Deficiencies to be Communicated”, and (3) final labeling.

III. Administrative

A. Reviewer's Signature

Xavier Ysern, PhD Review Chemist/ ONDQA/ DPAI/ Branch II

B. Endorsement Block

Ali Al-Hakim, PhD Branch Chief/ ONDQA/ DPAI/ Branch II

B. CC Block

Kati Johnson Project Manager/ OND/ ODE II/ DMEP

52 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process



CHEMISTRY REVIEW



□(sOP□&k4S□&17.27c66F 11-MAY-2009

FDA CDER EES

Page 1 of 4

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application : NDA 22418/000 Sponsor: MUTUAL PHARM
Org Code : 510 1400 SOUTH ORANGE AVE
Priority : SS ORLANDO, FL 32806

Stamp Date : 15-AUG-2008 Brand Name : FENOFIBRIC ACID TABS
PDUFA Date : 15-JUN-2009 35MG/105MG ORAL
Action Goal : Etab. Name:
District Goal : 16-APR-2009 Generic Name: FENOFIBRIC ACID TABS
35MG/105MG ORAL
Dosage Form: (TABLET)
Strength : 35 MG,105 MG

FDA Contacts: K. JOHNSON Project Manager 301-796-1234
Y. YANG Review Chemist 301-796-1777
S. TRAN Team Leader 301-796-1764

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

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile : CTL OAI Status: NONE
Last Milestone : OC RECOMMENDATION
Milestone Date : 10-SEP-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : FEI : b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile : CTL OAI Status: NONE
Last Milestone : OC RECOMMENDATION
Milestone Date : 10-SEP-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : FEI : b(4)

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER



CHEMISTRY REVIEW



11-MAY-2009

FDA CDER EES

Page 2 of 4

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Profile : _____ OAI Status: NONE
Last Milestone : INSPECTION SCHEDULED
Milestone Date : 07-MAY-09

b(4)

Establishment : CFN _____ FEI _____ b(4)

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile : CTL OAI Status: NONE
Last Milestone : OC RECOMMENDATION
Milestone Date : 10-SEP-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN _____ FEI _____ b(4)

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile : CTL OAI Status: NONE
Last Milestone : OC RECOMMENDATION
Milestone Date : 10-SEP-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 2523348 FEI : 2523348
MUTUAL PHARMACEUTICAL COMPANY, INC.
1100 ORTHODOX ST
PHILADELPHIA, PA 19124

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE MANUFACTURER

Profile : TCM OAI Status: NONE
Last Milestone : OC RECOMMENDATION
Milestone Date : 11-DEC-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN _____ FEI _____ b(4)

CHEMISTRY REVIEW

11-MAY-2009

FDA CDER EES

Page 3 of 4

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile : CTL OAI Status: NONE
Last Milestone : OC RECOMMENDATION
Milestone Date : 10-SEP-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : FEI : b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile : CTL OAI Status: NONE
Last Milestone : OC RECOMMENDATION
Milestone Date : 10-SEP-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : FEI : b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile : CTL OAI Status: NONE
Last Milestone : OC RECOMMENDATION
Milestone Date : 10-SEP-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : FEI : b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile : CTL OAI Status: NONE
Last Milestone : OC RECOMMENDATION
Milestone Date : 10-SEP-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : FEI : b(4)



CHEMISTRY REVIEW



11-MAY-2009

FDA CDER EES

Page 4 of 4

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

b(4)

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile : CTL OAI Status: NONE
Last Milestone : OC RECOMMENDATION
Milestone Date : 10-SEP-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

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

/s/

Xavier Ysern
5/18/2009 02:11:04 PM
CHEMIST

Ali Al-Hakim
5/18/2009 02:47:45 PM
CHEMIST

10/7/08

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

Division of Metabolism and Endocrinology Products

NDA: 22-418

Applicant: Mutual Pharmaceutical Company Inc.

Stamp Date: 15-AUG-2008

PDUFA Date: 15-JUN-2009

Proposed Proprietary Name: [none]

Established Name: Fenofibric acid

Dosage form and strength: Immediate release tablet –
35 mg and 105 mg

Route of Administration: oral

Indications: Treatment of hypercholesterolemia, mixed
dyslipidemia, and hypertriglyceridemia

PAL: Su (Suong) Tran, Branch II/DPA I/ONDQA

ONDQA Fileability: Yes

Comments for 74-Day Letter: Yes, on the last page.

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm/ClinPharm	<i>Not Applicable</i>
CDRH	<i>Not Applicable</i>
EA	Categorical exclusion request will be assessed by Primary Reviewer.
EES	EER was sent to Office of Compliance on 09-SEP-2008.
DMETS	<i>Labeling consult request will be sent as part of DMEP's request.</i>
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
Microbiology	<i>Not Applicable</i>
Pharm/Tox	<i>Not Applicable</i>

Summary: [See the discussion in Critical Issues later in this review.]

This is an electronic NDA, filed as a 505(b)(2) application. The RLD is TriCor (fenofibrate) Tablets.

The product is a single-entity, immediate-release tablet available in two strengths: 35 mg and 105 mg fenofibric acid. The drug substance is fenofibric acid. Fenofibric acid is the active moiety and primary metabolite of fenofibrate, which is the drug substance of the approved TriCor Tablets (different applicant). In vivo fenofibrate rapidly converts to fenofibric acid, which is responsible for the clinical effect.

The clinical proof of this product is from two pivotal bioequivalence (BE) studies, under fasted and fed conditions, using the 105 mg tablet and the RLD. A biowaiver request is made for the 35 mg dose, but the request may be for food effects studies because the 35 mg dose was used in the BE study R08-0057/MPC-028-08-1017 (this issue will be discussed with the ClinPharm team, and a decision will be made whether the biowaiver request will be handled by the ONDQA Biopharmaceutics Review Staff.)

Maximum daily dose is 105 mg fenofibric acid.

Route of administration	Oral
Dosage form	Immediate release tablet
Package type	35 mg: 30- and 60-count _____ bottles, and 90-count in _____ bottles 105 mg: 30-count in _____ bottles, 60-count in _____ bottles, and 90-count in _____ bottles
Potency	35 mg and 105 mg fenofibric acid
Color	White
Shape	35 mg: round 105 mg: oval
Coating	None.

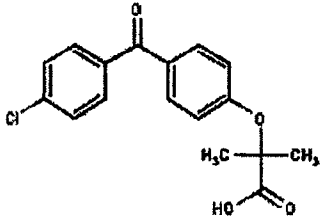
b(4)

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

Size	[unknown]
Scoring	None.
Imprint codes	35 mg: debossed "AR787" 105 mg: debossed "AR788"
Symbols	None.

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

Drug substance: fenofibric acid [See the discussion in Critical Issues later in this review.]

Chemical Structure	
Molecular Formula	C ₁₇ H ₁₅ ClO ₄
Relative Molecular Mass	318.75
CAS Registry Number	42017-89-0

2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoic acid

There is no chemistry, manufacturing, and controls information on the drug substance in the NDA. b(4)

Reference is made to the Drug Master File _____ held by _____. Fenofibric acid is a white crystalline powder that is insoluble in water. There are _____ and the drug substance is _____. b(4)
The proposed drug substance specification in the NDA is copied here. See the chemistry reviews of the DMF for additional details.

12 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

CHEMISTRY NDA FILEABILITY CHECKLIST

IS THE CMC SECTION OF APPLICATION FILEABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		All facilities are listed.
6	Has an environmental assessment report or categorical exclusion been provided?	X		Exclusion request per 21 CFR 25.31(b) is included.
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?	X		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?			Not applicable: not a parenteral

74-Day Letter – Draft Comments to the Applicant:

- Confirm that the manufacturing and testing facilities listed in Tables 2.3.S.4 and 2.3.P.7 are all the facilities involved in the manufacture and testing of the commercial drug substance and drug product.
- Provide the physical dimension of the finished tablets.
- Provide information on the physicochemical properties of the _____ of fenofibric acid and the impact of the _____, on the performance of the drug product. The information should cover aspects such as solubility, stability, dissolution _____ ratio, and effects on safety and efficacy.
- Provide references to the 21 CFR food additive regulations for the drug-contact components of the container closure systems used to package the drug substance and drug product.

b(4)

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/

Suong Tran
10/7/2008 03:46:49 PM
CHEMIST

as we discussed

Ali Al-Hakim
10/7/2008 04:16:13 PM
CHEMIST