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RESEARCH**

*APPLICATION NUMBER:*  
**22-418**

**MEDICAL REVIEW(S)**

Medical Officer 505(b)(2) NDA Review  
Division of Metabolism and Endocrine Products

6/10/09

**NDA-** 22-418

**IND-** 76, 749

**Name of Drug-** Fibracor

**Sponsor-** Mutual Pharmaceutical Company, Inc.

**Date of Submission-** August 15, 2008

**PDUFA Goal Date-** June 15, 2009

**Medical Reviewer-** Iffat N. Chowdhury, MD

**Background**

Mutual Pharmaceutical Company, Inc. (Mutual) is submitting this NDA under Section 505(b)(2) for its fenofibric acid tablets, Fibracor in doses of 35 mg and 105 mg, for the treatment of hypercholesterolemia and hypertriglyceridemia. Fenofibric acid is the active moiety of fenofibrate, a lipid-lowering drug first approved by Division of Metabolism and Endocrinology Products (DMEP) in 1993 as Lipidil®. Fenofibrate is currently available in a number of tablet and capsule formulations, including TriCor®, the chosen reference listed drug (RLD) for this NDA.

The proposed indications for Fibracor are identical to those currently approved for fenofibrate and include:

- Treatment of hypercholesterolemia, 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, specifically as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia.

The 35 mg and 105 mg doses of Fibracor are different from those listed in the initial IND application which were \_\_\_\_\_, and \_\_\_\_\_

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Appendix A summarizes the approved fenofibrate/fenofibric drug products. Although Tricor NDAs 19-304 and 21-203 were discontinued, reasons for discontinuation were not due to safety or efficacy concerns.

**Regulatory**

A Pre-NDA meeting between DMEP and Mutual to discuss the requirements for development and approval of fenofibric acid tablets was scheduled for 14 January 2008. The meeting was cancelled on 11 January 2008 as agreement was reached through written preliminary responses. It was agreed that a bioequivalence study demonstrating a

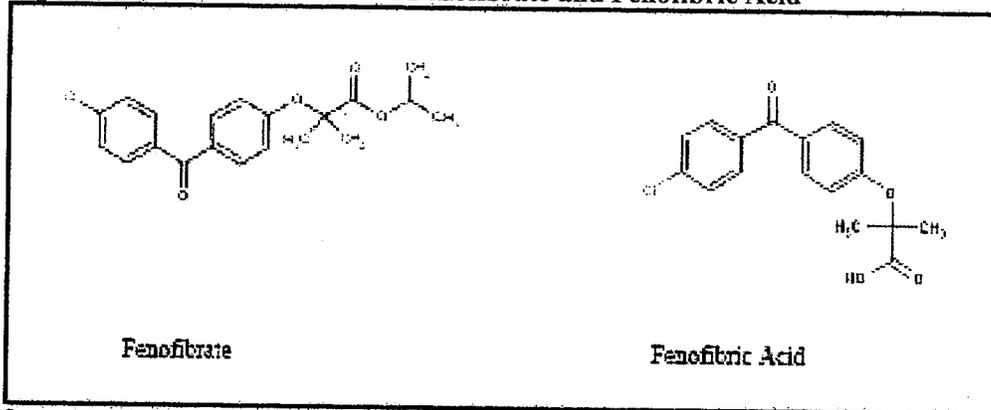
comparable rate and extent of absorption of Mutual's fenofibric acid tablets with the reference listed fenofibrate product, a drug-drug interaction study with efavirenz, a CYP2B6 inhibitor, and a thorough review of the publicly available safety information for fenofibrate would be submitted under the NDA.

Information to support a biowaiver for Fibricor 35 mg was a topic of discussion in the pre-NDA briefing package (IND 76,749 Serial No. 013, submitted 4 December 2007, Question #9). Specifically, Mutual proposed to support the biowaiver request of the 35 mg fenofibric acid tablets based on composition proportionality and similar dissolution profiles. The official pre-NDA meeting responses, dated 15 January 2008 stated that the proposal was acceptable if pharmacokinetic linearity of fenofibric acid was demonstrated over the proposed dose range.

### Drug in Study

The chemical name of the drug substance is 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropionic acid. The chemical structures of fenofibrate and fenofibric acid are depicted below.

**Figure 1: Chemical Structures of Fenofibrate and Fenofibric Acid**



Source: Mutual NDA

The drug product, Fibricor, is a fenofibric acid tablet in 35 mg and 105 mg formulations. Excipients are as follows in the table below.

**Table 1: Composition of Fibracor (Mutual's Fenofibric Acid)**

Ingredient	% w/w	Tablet Strength	
		35 mg	105 mg
		mg/Tablet	
Fenofibric acid		35.0	105.0
Microcrystalline cellulose, NF			
Copovidone, NF			
Croscopovidone, NF			
Magnesium stearate, NF			
Total			

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Source: Study Report, Section 2.3P Drug Product.

**Biopharmaceutical Studies Submitted to NDA 22-418**

Biopharmaceutical studies were reviewed in detail by Dr. Immo Zdrojewski from the Office of Clinical Pharmacology. Fifteen studies were submitted under the IND including 1 dose proportionality study, 5 in vitro and 1 in vivo drug-drug interaction studies and 8 biopharmaceutics studies, including a fasted, and a fed BE study, and a food effect study. Five biopharmaceutical studies were the focus of the review by clinical pharmacology and are summarized in the table below.

**Table 2: Biopharmaceutical Studies with 105 mg or 35 mg Fibracor**

Type of Study	Objectives of Study	Study Design and Type of Control	Test Product	Number of Subjects	Duration of Treatment
<b>BA, Food Effect Study (MPC-028-07-1009)</b>	To compare the rate and extent of absorption and to evaluate the safety and tolerability of a single 105-mg dose of fenofibric acid in healthy adult volunteers administered with a low-fat meal, standard meal, and highfat/ high-calorie meal and in the fasted state	Four-period, crossover, open-label	105 mg	37 (34 completed)	Single dose
<b>Comparative BA/BE (MPC-028-07-1007)</b>	To evaluate the bioequivalence of fenofibric acid tablets, 105 mg (Mutual) relative to TriCor® Tablets (145 mg by Abbott Pharmaceuticals, Inc.) in healthy adult volunteers when each is administered under fasted conditions.	Two-period, crossover	105 mg	54	Single dose
<b>Comparative BA/BE (MPC-028-07-1008)</b>	To evaluate the bioequivalence of fenofibric acid tablets, 105 mg (Mutual) relative to TriCor® Tablets (145 mg, Abbott) when each was administered following a	Two-period, crossover	105 mg	47	Single dose

Type of Study	Objectives of Study	Study Design and Type of Control	Test Product	Number of Subjects	Duration of Treatment
	breakfast of standard composition (fed state).				
<b>Comparative BA/BE and Pharmacokinetic Dosage Form Proportionality (MPC-028-07-1017)</b>	To evaluate the pharmacokinetic linearity and bioequivalence of fenofibric acid over a single dose range of 35 to 105 mg when administered to healthy adult volunteers under fasted conditions.	Three-period, crossover	35 and 105 mg	54	Single dose
<b>Extrinsic Factor</b>	To determine the effect of multiple doses of fenofibric acid (steady-state) on the pharmacokinetics of single-dose efavirenz in healthy adult subjects.	One-sequence, open-label, drug interaction study	105 mg	24	Ten days

Source: Section 5.2, Mutual NDA.

*Bioequivalence*

According to Dr. Zdrojewski's review, the results from Study MPC-028-07-1007 demonstrate that Mutual's 105 mg fenofibric acid tablets are bioequivalent to Abbott's Tricor® 145 mg tablets under fasted conditions. The geometric mean ratios of  $AUC_{inf}$ ,  $AUC_{0-last}$ , and  $C_{max}$ , and the 90% confidence intervals for these ratios meet the bioequivalence criteria (Table 3).

Table 3 Study MPC-028-07-1007: Statistical Summary (Geometric means, ratio of means, and 90% confidence intervals) Ln-transformed data (N=49)

Parameter	Fenofibric Acid Tablets (105 mg)	TriCor® Tablets (145 mg)	% Ratio	90% CI
$AUC_{0-t}$ ( $\mu\text{g}\cdot\text{hr}/\text{mL}$ )	148.59371	158.70070	93.63	(91.28, 96.05)
$AUC_{0-\infty}$ ( $\mu\text{g}\cdot\text{hr}/\text{mL}$ )	162.95683	173.93396	93.69	(91.67, 95.75)
$C_{max}$ ( $\mu\text{g}/\text{mL}$ )	12.00135	10.65025	112.69	(107.99, 117.59)

Source: I. Zdrojewski, Clinical Pharmacology Review, pg.5.

In Study MPC-028-07-1008, Mutual evaluated the bioequivalence of the 105 mg fenofibric acid tablets to Tricor under fed conditions. According to the clinical pharmacology review, the geometric mean ratios  $AUC_{0-inf}$ ,  $AUC_{0-last}$ , and  $C_{max}$ , and the 90% confidence interval for fenofibric acid fall wholly within 80-125% of the reference product (Table 4). The rate and extent of exposure was approximately 10% lower for Fibracor as compared to Tricor.

Table 4 Study MPC-028-07-1008: Summary Statistics of fenofibric acid tablets vs. Tricor® following a standard breakfast

Geometric Means, Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Fenofibric Acid N=47				
Parameter	Fenofibric Acid Tablets (105 mg)	TriCor® Fenofibrate Tablets (145 mg)	% Ratio	90% CI
$AUC_{0-t}$ ( $\mu\text{g}\cdot\text{hr}/\text{mL}$ )	113.62538	123.91562	91.70	(89.73, 93.7)
$AUC_{0-\infty}$ ( $\mu\text{g}\cdot\text{hr}/\text{mL}$ )	124.88596	137.01609	91.15	(89.08, 93.26)
$C_{max}$ ( $\mu\text{g}/\text{mL}$ )	8.36916	9.30079	89.98	(86.78, 93.31)

Source: I. Zdrojewski, Clinical Pharmacology Review, pg.5.

According to Dr. Zdrojewski's review, Fibracor's pharmacokinetics are influenced by food. When administered with a low fat meal, the  $C_{max}$  is approximately 20% lower, when administered with a high fat/high calorie meal; the  $C_{max}$  is approximately 35% lower. However, the decrease in maximum exposure with a lack of difference in total exposure may not be clinically relevant. According to the clinical pharmacology review, Mutual's 105 mg fenofibric acid tablets are bioequivalent to the reference listed drug under fasted and standardized fed conditions.

#### *Dosage Form Proportionality*

In Study MPC-028-07-101, Fibracor 35 mg tablets showed dosage form proportionality to the 105 mg tablets when pharmacokinetic parameters are evaluated as dose adjusted to Fibracor 105 mg, and when the 35 mg tablets are given as 3x35mg. The 90% confidence intervals for the geometric mean ratios for the 1x35 mg adjusted to 105 mg and the 3x35 mg fall within the bioequivalence criteria of 80-125% when compared to the 105 mg tablet.

#### *Drug-Drug Interaction*

Fibricor 105 mg tablets did not show a clinically relevant interaction with efavirenz, a CYP2B6 substrate. Total exposure of efavirenz, when administered with fenofibric acid at steady state, are approximately 10 to 11 % lower than efavirenz administered alone.

In summary, the clinical pharmacology reviewer had found that Fibricor 105 mg is bioequivalent to Tricor 145 mg. In addition, a dose of 3 x 35 mg tablets is bioequivalent to a 105 mg tablet.

### **Summary of Safety**

With this 505(b)(2) application, Mutual is relying on prior safety experience with Tricor®. Mutual also conducted a review of safety information for fenofibrates in published literature and the FDA and WHO pharmacovigilance databases. Information from the Tricor label as well as non-pooled safety data from Mutual-sponsored pharmacokinetic studies was also included.

This review evaluated only data from the non-pooled Mutual-sponsored studies. Articles from the literature and the FDA and WHO databases had no CRFs available. These sources are included in this review as a general overview of supplemental information on fenofibrates.

Source	Population	N	Data Source / Study Design
<b>Tricor Approved Labeling (NDA 21-656)</b>			
Latest revision	--	--	Revised January 2008
<b>Mutual-Sponsored Pharmacokinetic Studies (N=10 Studies)</b>			
<i>Open-Label, Single Dose Studies</i>			
MPC-028-06-1001	Healthy adults	20	Randomized, crossover study comparing 50-mg, 90 mg, and 130-mg fenofibric acid tablets (Mutual) with fenofibrate 145 mg tablets (TriCor®, Abbott Laboratories) under fasting conditions
MPC-028-07-1002	Healthy adults	9	Randomized, crossover study 90-mg and 130-mg fenofibric acid tablets with 145-mg fenofibrate tablets (TriCor®) under fed conditions
MPC-028-07-1005	Healthy adults	18	Randomized, crossover study comparing fenofibric acid tablets, 90 mg (Mutual) after a low-fat meal or a standard meal with fenofibrate (TriCor®) 145-mg tablets after a standard meal
MPC-028-07-1006	Healthy adults	18	Randomized, crossover study comparing 130-mg fenofibric acid tablets (Mutual) under fed and fasted conditions with fenofibrate 145-mg tablets (TriCor®) under fasted conditions
MPC-028-07-1007	Healthy adults	54	Randomized, crossover study comparing 105-mg fenofibric acid tablets (Mutual) with fenofibrate 145-mg tablets (TriCor®) under fasted conditions
MPC-028-07-1008	Healthy adults	54	Randomized, crossover study comparing 105-mg fenofibric acid tablets (Mutual) with fenofibrate 145-mg tablets (TriCor®) under fed conditions (standard meal)
MPC-028-07-1009	Healthy adults	37	Randomized, crossover comparing 105 mg fenofibric acid tablets (Mutual) under fasted and fed (low-fat, standard, and high-fat/high-calorie meals) conditions
MPC-028-07-1016	Healthy adults	18	Randomized, crossover study comparing 105-mg fenofibric acid capsule (Mutual) with fenofibrate 145 mg tablets (TriCor®, Abbott Laboratories) under fasting conditions and the effect of food on Mutual's product
MPC-028-08-1017	Healthy adults	54	Randomized, crossover study dose proportionality study of Mutual's fenofibric acid tablets under fasting conditions (1 × 35-mg, 3 × 35-mg [105 mg total], and 1 × 105-mg)
<i>Multiple Dose Studies</i>			
MPC-028-08-1018	Healthy adults	30	Non-randomized, one-sequence, drug interaction study to determine fenofibric acid (steady-state, 105 mg/day × 10 days) on the pharmacokinetics of single-dose efavirenz (concurrently on Day 10).
<b>Medical Literature</b>			
Published articles or case reports	Therapeutic use	--	32 publications
<b>Postmarketing Safety Data</b>			
U.S. Food and Drug Administration	Primarily U.S. but includes foreign reports	--	1130 reports for fenofibrate in the AERS database as of 31 December 2007 (the extent of information publicly available as of 25 June 2008)
World Health Organization	82 countries including the U.S.	--	3272 reports in the VigiBase database as of 27 June 2008

Source: Mutual NDA 22-418, ISS.

### *Mutual-Sponsored Studies*

Mutual conducted 10 pharmacokinetic studies in which 312 healthy volunteers were exposed to at least one dose of fenofibrate or fenofibric acid. Of these, 282 subjects (approximately 90%) received single doses (Mutual's fenofibric acid tablets (35-, 50-, 90-, 105-, or 130-mg) or capsules (105-mg) or TriCor® 145-mg tablets, and 30 subjects received Fibracor 105-mg tablets once daily for 10 days (approximating steady state).

Across the single-dose studies, which involved 282 subjects with two to four dosing periods, 71 subjects (25.2%) reported at least one adverse event. There are no clear trends to more events at the highest dose (130 mg) or between fenofibric acid and fenofibrate. Headache is the most commonly reported event (9.2%), treatment related in most cases. The only other adverse events that occurred in  $\geq 5$  subjects (2 to 3% of subjects) were dizziness, pharyngolaryngeal pain, and back pain. None appeared related to treatment.

In study MPC-028-07-1007 (Comparative BE study), there was one serious adverse event (subject #4), a spontaneous abortion, which occurred on \_\_\_\_\_ The positive pregnancy test occurred 7 days after the subject had received Tricor® 145 mg. She was discontinued and subsequently miscarried. Subject #45 discontinued due to a streptococcal rash which occurred 4 days after receiving fenofibric acid 105 mg.

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In study MPC-028-08-1017 (Fibracor 105 mg/day  $\times$  10 days + Efavarinz concurrently on day 10) the most common adverse events (not associated with efavirenz) were headache (14.3%), nausea and vomiting (10.3%), and pyrexia and stomach discomfort (7.1%). Two subjects reported adverse events of interest; subject #4 had elevated creatinine phosphokinase on Day 31 to a level of 1440 IU/L, which decreased to 239 IU/L and subject #10 had AST and ALT  $>6\times$ ULN (AST=371, ALT= 112, TB=1.3). Liver enzymes were decreasing (AST=47, ALT=34) on latest laboratory draw.

In study MPC-028-07-1008 (Comparative BE study in fed state) the most common AE was blood creatine phosphokinase increased, occurring in 4 subjects (7.4%). Three of the four subjects with increased CPK were on fenofibric acid 105 mg; CPK elevations were 396 IU/L (Subject #27), CPK 1,133 IU/L (Subject #10) which decreased to 286 IU/L, and 524 IU/L (Subject #44). One subject on Tricor 145 mg had CPK elevation to 619 IU/L.

Overall, adverse events occurring in the 10 Mutual-sponsored pharmacokinetic studies were consistent with what is known about the safety of fenofibrate based on review of the approved labeling for Tricor.

### *Published Literature and Tricor Label*

Mutual used the approved Tricor® product labeling as the primary basis for safety information. Mutual also supplemented its safety review with additional publications of safety-related information on fenofibrate. Mutual conducted an initial search of the

worldwide literature on 31 October 2006 and updated on 12 June 2008. The following databases were searched:

- MEDLINE-1950 to present
- EMBASE-1974 to present
- Biosis Previews- 1926 to present
- JICST-Eplus- 1985 to 2007

In total, 549 citations were identified and 32 publications were included in the Summary of Safety. According to the applicant, no new unlabeled safety information was identified.

#### *Analysis of Adverse Event by System Organ Class*

The events affecting the liver, musculoskeletal, cardiovascular, gastrointestinal and skin and appendages systems are discussed below, as these are among the most prominent events that occur while patients are on fenofibrate. There was no new safety information found in any other system organ class other than that already in the Tricor label.

#### *Liver Function*

The most common adverse events with fenofibrate treatment are liver function test abnormalities and increased transaminases. In a pooled analysis of 10 placebo-controlled trials described in the approved labeling for Tricor, increases to  $\geq 3$  times the upper limit of normal occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo. Values generally return to within normal limits with continued treatment and after stopping fenofibrate. However, hepatocellular, chronic active, and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.

The literature search conducted by Mutual identified three cases of hepatitis (Couzigou et al., 1980, Baumann, 1994, and Ho Chiu-Yung et al., 2004) and one review of risk factors for increased liver function tests results in fenofibrate-treated patients (Hayakawa et al., 2002). However, based on information presented in these publications, currently no additional safety information needs to be addressed in the product labeling for Mutual's fenofibric acid.

#### *Musculoskeletal System*

As described in the Warnings section of the TriCor® labeling, fenofibrate may be associated with increased creatine phosphokinase and myopathy. On rare occasions, treatment with drugs of the fibrate class has been associated with rhabdomyolysis, usually in patients with impaired renal function. Also, the use of fibrates alone may occasionally be associated with myositis and myopathy.

The following have been reported during post-marketing surveillance or by three or more patients in placebo-controlled trials or reported in other controlled or open trials: arthralgia, arthritis, arthrosis, bursitis, joint disorder, leg cramps, myalgia, myasthenia, myositis, rhabdomyolysis, and tendosynovitis.

The literature search conducted by Mutual identified three publications describing 4 patients developing rhabdomyolysis secondary to fenofibrate use for 3 weeks to 2 years (Tahmaz et al., 2007; Duda- Krol et al., 2000; Clouatre et al., 1999). There was one additional report of fenofibrate-induced myopathy, presenting as muscle pain and quadriplegia following exposure for 35 days (Ghosh et al., 2004). All events resolved upon discontinuation of drug. Based on information presented in these publications, no additional safety information needs to be addressed in the product labeling.

As described in the Warnings section of the approved labeling, the combined use of fenofibrate and HMG-CoA reductase inhibitors (statins) has been associated, in the absence of a marked pharmacokinetic interaction, with reports of rhabdomyolysis, markedly elevated creatine kinase levels, and myoglobinuria, leading to acute renal failure in a high proportion of cases.

One publication (Alsheikh-Ali et al., 2004) summarized cases reported to the FDA's post-marketing safety database. From 1999 to 2002, there were 68 reports of rhabdomyolysis submitted to FDA, compared with 1304 reports for gemfibrozil. Rates of rhabdomyolysis were significantly higher with gemfibrozil compared with fenofibrate (gemfibrozil prescriptions versus fenofibrate prescriptions, odds ratio 10.84, 95% confidence interval 8.44 to 13.95,  $p < 0.000001$  [chi square]). This difference appeared to be driven largely by an increased risk in patients taking gemfibrozil concomitantly with HMG-CoA reductase inhibitors, particularly cerivastatin. The use of fenofibrate in combination with an HMG-CoA reductase inhibitor results in fewer reports to FDA of rhabdomyolysis per million prescriptions dispensed than does the use of gemfibrozil (Jones et al., 2005). Concomitant use of gemfibrozil and an HMG-CoA reductase inhibitor has been shown to result in higher plasma concentrations of HMG-CoA reductase inhibitor as gemfibrozil inhibits the glucuronidation of statins and CYP2C8, which is responsible for cerivastatin metabolism.

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Fenofibrate has not been shown to have a major effect on the pharmacokinetic profile of simvastatin, rosuvastatin, pravastatin, or atorvastatin. According to the Trilipix® PI, effects of fenofibric acid or fenofibrate co-administration on the systemic exposure of the following drugs are as follows: rosuvastatin (↑AUC 6%, Cmax ↑20%), atorvastatin (↓AUC 17%, 0% Cmax), pravastatin (↑AUC 28%, ↑Cmax 36%), and simvastatin (↓AUC 11%, ↓Cmax 17%).

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study in which patients on fenofibrates were allowed concomitant statin therapy reinforces the available data on the safety of fenofibrate-statin combination therapy. Furthermore, the Agency has recently approved Trilipix, a fenofibric acid, in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk

equivalent who are on optimal statin therapy to achieve their LDL-C goal. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is expected to provide additional long-term safety information on the combined use of statins with fenofibrate therapy.

#### *Cardiovascular System*

Although coronary heart disease risks are not discussed in Mutual's Safety Summary, this clinical reviewer notes the WARNINGS AND PRECAUTIONS section of the Tricor labeling discusses the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. The FIELD study was a 5 year randomized, placebo-controlled study of 9795 patients with type 2 diabetes mellitus treated with fenofibrate. Fenofibrate demonstrated a non-significant 11% relative reduction in the primary outcome of coronary heart disease events (HR 0.89, 95% CI 0.75-1.05, p=0.16) and a significant 11 % reduction in the secondary outcome of total cardiovascular disease events (HR 0.89 (0.80-0.99), p=0.04). There was a non-significant 11 % increase (HR 1.11 (0.95, 1.29), p=0.18) in total heart disease mortality and 19% increase (HR 1.19 (0.90, 1.57), p=0.22) in coronary heart disease mortality with fenofibrate as compared to placebo.

The risk of venothromboembolic disease is also discussed in the Precautions section of the current approved labeling for Tricor. In the FIELD trial, deep vein thrombosis (DVT) and pulmonary embolus (PE) were observed at higher rates in the fenofibrate than the placebo-treated group. For DVT, there were 48 events (1%) in the placebo group and 67 (1%) in the fenofibrate group (p = 0.074); and for PE, there were 32 (0.7%) events in the placebo group and 53 (1%) in the fenofibrate group (p = 0.022).

In the Coronary Drug Project, a higher proportion of patients in the clofibrate group experienced definite or suspected fatal or nonfatal PE or thrombophlebitis than the placebo group (5.2% versus 3.3% at 5 years; p < 0.01).

The following have been reported during post-marketing surveillance or by three or more patients in placebo-controlled trials or reported in other controlled or open trials and is described in the current Tricor labeling: angina pectoris, arrhythmia, atrial fibrillation, cardiovascular disorder, coronary artery disorder, electrocardiogram abnormal, extrasystoles, hypertension, hypotension, migraine, myocardial infarct, palpitation, peripheral vascular disorder, phlebitis, tachycardia, varicose vein, vascular disorder, vasodilatation, venous thromboembolic events (deep vein thrombosis, pulmonary embolus), and ventricular extrasystoles.

#### *Gastrointestinal System*

As described in the Warnings section of the current TriCor® label, fenofibrate may increase cholesterol excretion into the bile, leading to cholelithiasis.

The literature search conducted by Mutual identified one case report of a patient with hyperlipidemia treated with fenofibrate in whom a gallbladder stone was detected by computed tomography 3 months after starting therapy (Inuzuka et al., 2003). Fenofibrate was stopped without resolution.

As described in the Warnings section of the approved TriCor® labeling, pancreatitis has been reported in patients taking fenofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation from obstruction of the common bile duct.

Although not reported in short-term efficacy studies, pancreatitis occurred in 0.8% of fenofibrate-treated patients in a long-term study as compared to 0.5% of placebo patients (FIELD Study Investigators, 2005). The difference was small but statistically significant ( $p = 0.031$ , chi square test). No published case reports of pancreatitis associated with the use of fenofibrate were identified by the literature search.

As described in the approved TriCor® labeling, the following have been reported during postmarketing surveillance or by three or more patients in placebo-controlled trials or reported in other controlled or open trials: anorexia, cholecystitis, cholelithiasis, colitis, diarrhea, duodenal ulcer, dyspepsia, eructation, esophagitis, flatulence, gastritis, gastroenteritis, gastrointestinal disorder, increased appetite, jaundice, liver fatty deposit, nausea, pancreatitis, peptic ulcer, rectal disorder, rectal hemorrhage, tooth disorder, and vomiting.

#### *Skin and Appendages*

The Precautions section of the current TriCor® labeling states that acute hypersensitivity reactions including severe skin rashes requiring hospitalization and treatment with corticosteroids have occurred rarely during treatment with fenofibrate, including spontaneous reports of Stevens-Johnson syndrome and toxic epidermal necrolysis (incidence not given). Urticaria was seen in 1.1% versus 0% and rash in 1.4% versus 0.8% of fenofibrate and placebo patients, respectively, in controlled trials.

In addition to the events noted above, the following are described in the approved TriCor® labeling as having been reported during post-marketing surveillance or by three or more patients in placebo-controlled trials or reported in other controlled or open trials: acne, alopecia, contact dermatitis, eczema, fungal dermatitis, herpes simplex, herpes zoster, maculopapular rash, nail disorder, photosensitivity reaction, pruritus, rash, sweating, skin disorder, and skin ulcer.

The literature search conducted by Mutual identified several case reports describing photosensitization by fenofibrate producing erythematovesicular or eczematous eruptions (Carsuzaa et al., 1994; Serrano et al., 1992). Two other published studies examined the basis for this reaction (Bosca et al., 1999; Miranda et al., 1994), confirming that the

photosensitivity of fenofibric acid is attributable to the benzophenone moiety. Photosensitivity reaction is a labeled adverse event.

#### *Laboratory Abnormalities*

As described in the Precautions section of the current TriCor® labeling, elevations in serum creatinine have been reported in patients on fenofibrate. These elevations tend to return to baseline following discontinuation of fenofibrate. The clinical significance of these observations is unknown. Additionally, blood urea nitrogen increased has been reported during post-marketing surveillance or placebo-controlled or other controlled or open trials.

There are published reports of clinically relevant increases in serum creatinine levels associated with fenofibrate, most recently reviewed by McQuade et al. (2008). Mean increases in serum creatinine levels range from 12 to 36%. Risk factors include pre-existing chronic renal disease, drugs that affect renal dynamics, and kidney or liver transplant. Of 9,795 patients enrolled in the FIELD trial (Keech et al., 2005), which excluded patients with a baseline serum creatinine > 1.5 mg/dL, median serum creatinine levels at the end of the study were significantly higher in the fenofibrate-treated group compared with those in the placebo group (1.03 mg/dL versus 0.9 mg/dL, respectively;  $p < 0.001$ ).

As described in the approved TriCor® labeling, fenofibrate reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid. The literature search identified one publication reporting 2 cases in which long-term administration of fenofibrate for hyperlipidemia was associated with marked and sustained reductions in serum uric acid and acute gout attacks (Hepburn et al., 2003).

#### *Post-marketing Safety Database*

##### *FDA Database*

According to Mutual, as of 31 December 2007, there were an estimated 1130 MedWatch reports in which fenofibrate are listed as a primary or secondary suspect drug. This estimate may include duplicates as it was obtained by adding the number of individual reports from the ADR and AERS databases.

A summary of the most common adverse events reported with fenofibrate, listed by database, is presented in the table below. This list of events includes clinical laboratory adverse events as they are among the most commonly reported adverse events.

**Table 7: Adverse Events with Fenofibrate FDA Database**

FDA ADR Database $\geq 2$ reports (1969 – Oct 1997) COSTART Term	No. Reports	FDA AERS Database $\geq 30$ reports (Nov 1997 – Dec 2007) MedDRA Preferred Term	No. Reports
Total	22	Total	1108
Hepatitis	4	Rhabdomyolysis	116
Liver function tests abnormal	4	Blood creatine phosphokinase increased	87
Allergic reaction	2	Myalgia	83
Antinuclear antibody present	2	Renal failure acute	80
Dyspnea	2	Drug interaction	68
Epidermal necrolysis	2	Pyrexia	57
Fever	2	Alanine aminotransferase increase	55
Gamma glutamyl transpeptidase inc	2	Arthralgia	53
Gastrointestinal disorder	2	Aspartate aminotransferase increase	51
Rash	2	Malaise	51
Suicide attempt	2	Blood creatinine increased	42
		Weight Decreased	42
		Pruritus	41
		Asthenia	40
		Renal failure	36
		Drug interaction NOS	35
		International Normalised ratio increased	35
		Fatigue	34
		Condition Aggravated	30

Source: Mutual NDA 22-418.

*WHO Database*

According to Mutual, reports of adverse events for fenofibrate submitted to the World Health Organization (WHO) have been obtained. The reports come from a variety of sources including both regulatory and voluntary sources and are not, therefore, entirely spontaneous. The WHO summary of safety for fenofibrate showed 3272 reports submitted between 1968 and June 2008.

Overall these reports are consistent with the most information summarized for fenofibrate. The most common adverse events from the WHO database are summarized below.

Table 8: Adverse Events with Fenofibrate WHO Database

WHO 1968 – June 2008 Adverse Event Term	No. Reports
Total	3727
Myalgia	332
Creatine phosphokinase increased	223
SGPT increased	206
SGOT increased	188
Rhabdomyolysis	160
Hepatitis	150
Photosensitivity reaction	134
Pruritus	133
Azotaemia	123
Abdominal pain	119
Pancreatitis	107
Rash erythematous	97
Rash	95
Nausea	92
Asthenia	85
Arthralgia	80
Hepatic function abnormal	75
Hepatic enzymes increased	69
Diarrhoea	68
Urticaria	67
Headache	61
Renal failure acute	59
Fever	58
Fatigue	56
Gamma GT increased	55
Rash maculo-papular	54
Renal function abnormal	51

Source: Mutual NDA 22-418.

### SAFETY UPDATE

Mutual submitted a second version of the ISS on 10 December 2008 which incorporated the 120-day Safety Update. The applicant conducted another literature search with a cut-

off date of 18 November 2008. There were no unknown risks identified in the safety update.

## **AUDITS**

A DSI audit of Study MPC-028-07-1007 found that PRACS Institute-Cetero Research failed to report one miscarriage to the IRB. A second violation asserts that the firm changed 50 of the 54 case report forms (CRFs) from being study eligible to being ineligible without clarification more than 8 months after study completion. On 21 May 2009, this clinical reviewer requested a tabulation of the all the deviations and a justification as to why the patient data should be included in the review.

On 4 June 2009, Mutual submitted a response the citation. The full submission is attached to this clinical review as Appendix B with the following as an excerpt from this document.

**“PRACS Institute-Cetero Research (PRACS) conducted MPC-028-07-1007 for Mutual Pharmaceutical Company, Inc. (Mutual). As part of their procedure, they directly transcribed the inclusion and exclusion criteria in the protocol to an Eligibility Checklist case report form.**

The inclusion criterion that accounted for the protocol deviation affecting the 50 subjects noted above was stated as follows:

**“Medically healthy on the basis of medical history, physical examination, clinical laboratory test results (especially tests for renal and hepatic function) within the normal range, and no clinically significant vital sign measurements and ECG parameters, as deemed by the Medical Investigator.”**

During the conduct of the study, the clinical staff and Medical Investigator interpreted the above inclusion criterion as allowing the Medical Investigator to exercise clinical judgment as to the significance of any abnormality, including clinical laboratory test results. None of the values outside laboratory reference range were judged by the Medical Investigator as clinically significant and few warranted repeat. Thus, subjects with values outside reference range were enrolled as medically healthy with non-clinically significant laboratory values.

**It had been the Mutual’s intent that the phrase “as deemed by the Medical Investigator” applied only to the vital sign and ECG measurements. Therefore, laboratory deviations would need to be approved by Mutual. As Mutual was not consulted and thus, did not approve these protocol deviations, the subjects with results outside laboratory reference range were identified in the clinical study report as having violated the protocol. During study report preparation, these laboratory deviations were reviewed and it was concluded that they did not affect the pharmacokinetics of fenofibric acid.”**

This clinical reviewer and the clinical pharmacology reviewer, Dr. Immo Zdrojewski, have reviewed the laboratory deviations in the 50 patients in study MPC-028-07-1007. The subjects were healthy and the deviations were minor with no hepatic or renal dysfunction. None of the laboratory deviations presented a safety hazard and would not be expected to affect the pharmacokinetics of fenofibric acid.

### CMC

The following is an excerpt from Dr. Houda Mahayni's review for the biowaiver assessment for Fibracor 35 mg tablets.

According to Mutual, bioequivalence of the 105 mg fenofibric acid tablet with TriCor® 145 mg, was demonstrated in two single-dose studies performed in healthy adult subjects under fasted and fed conditions. Additionally, pharmacokinetic linearity was demonstrated over the dose range 35-105 mg. Therefore, Mutual requested a "biowaiver" of any further in vivo studies for the 35 mg fenofibric acid tablet based on the 35 mg fenofibric acid tablet being compositionally proportional to the 105 mg fenofibric acid tablet, and the in vitro dissolution profiles of both strengths being similar using suitable methodology.

Although the 35 mg fenofibric acid tablet is compositionally proportional to the 105 mg fenofibric acid tablet, the comparative dissolution results of fenofibric acid tablets (35 mg vs. 105 mg) in three media show similarity in only one media (0.1 N HCl),  $f_2 > 50$ . The dissolution profile were not similar in the other two media tested (water and pH 4.5 acetate buffer),  $f_2 < 50$ . Therefore, the information provided in this submission on its own merit does not support the biowaiver request.

However, the sponsor submitted a clinical study report (MPC-028-08-1017) to evaluate the pharmacokinetic linearity of fenofibric acid over a single dose range of 35 to 105 mg, and to compare drug composition proportionality of three 35 mg fenofibric acid tablets (total 105 mg single dose) to a single 105 mg fenofibric acid tablet in healthy adult volunteers when each is administered under fasted conditions.

According to the Clinical Pharmacology reviewer, Dr. Immo Zdrojewski, the sponsor demonstrated that comparison of three Mutual's fenofibric acid tablets, 35 mg to a one Mutual's fenofibric acid tablets; 105 mg in the fasting state are bioequivalent. Administration of three of Mutual's fenofibric acid tablets, 35 mg and one of Mutual's fenofibric acid tablets, 105 mg resulted in C<sub>max</sub> and AUC for which the 90% confidence intervals (CI) were within the bioequivalence interval of 80 to 125% which indicates the two treatments are bioequivalent.

b(4)

## PHARMACOLOGY/TOXICOLOGY

No pharmacology/toxicology deficiencies were identified. The pharm/tox review indicates there are no novel excipients present in the drug product that would require non-clinical characterization.

## FINANCIAL DISCLOSURE

The sponsor provided a signed form FDA 3454, certifying that no financial arrangements or interests were held by the listed clinical investigators for the clinical pharmacology studies conducted to support approval of this application.

## LABELING

A detailed labeling review will be conducted separately from this document.

## PROPRIETARY NAME

Mutual has requested a review on the acceptability of the tradenames Fibracor vs.           . The Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Fibracor. This clinical reviewer is in agreement with the Division of Drug Marketing, Advertising, and Communication (DDMAC) in its assessment of no objection to the proposed name, Fibracor, from a promotional perspective.

b(4)

## PEDIATRIC STUDY REQUIREMENTS

Mutual has requested a pediatric waiver for its fenofibric acid. Per the applicant, the drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients as primary intervention focuses on changing the diet.

Other approved fenofibrates (NDAs 19-304, 21-350, 21-612, and 21-695), including the RLD, Tricor (NDA 21-656), have received pediatric waivers.

This reviewer is in agreement with the request. Pharmacologic intervention is recommended for children  $\geq 8$  years of age with an LDL concentration of  $> 190$  mg/dL (or  $> 160$  mg/dL with a family history of early heart disease or two or more additional risk factors present or  $\geq 130$  mg/dL if diabetes mellitus is present) where diet alone is insufficient to reduce hyperlipidemia. There are several classes of medication available as adjunctive treatment to diet. The drug classes of first choice are bile acid sequestrants or HMG-CoA reductase inhibitors. Fibrates are not recommended for routine use in children.

## **RECOMMENDATIONS**

This reviewer recommends approval of this 505(b)(2) fenofibric acid, Fibracor. Labeling should reflect the recently approved fenofibric acid, Trilipix and Tricor, the RLD.

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**APPENDIX A**

**Table: Previously Approved Fenofibrate/Fenofibric Drug Products**

Trade Name	NDA (Date of Approval)	Dosage Strengths (mg)	Dosage Form	RLD	Comments
Lipidil®	NDA 19,304 (31 Dec 93)	100	Capsule		Approved for hypertriglyceridemia based on two placebo-controlled trials (100 mg t.i.d.); give with meals
	NDA 19,304 / S001 (9 Feb 98)	67			Approval based on bioequivalence to 100 mg capsule; give with meals
TriCor®	S003 (30 Jun 99)	67, 134, 200	Capsule (micronized)	No (DC'd)	Approval based on bioequivalence between 200 and 3×67 mg capsules; available in generic form (ANDA 75,753, Teva; 200 mg = RLD); give with meals
	S-005 (24 Apr 00)	67, 134, 200			Approval for elevated LDL-C, Total-C, triglycerides, and Apo B in primary hypercholesterolemia or mixed dyslipidemia on basis of four placebo controlled trials; give with meals
TriCor®	NDA 21,203 (4 Sep 01)	54, 160	Tablet	No (DC'd)	Available in generic forms, including 107 mg (ANDA 76,433, Teva 160 mg = RLD); give with meals
Triglide™	NDA 21,350 (7 May 05)	50, 160	Tablet	No	Approval based on bioequivalence of 160 mg tablet to TriCor® (200 mg micronized capsule); administer with or without food
Lipofen™	NDA 21,612 (11 Jan 06)	50, 100, 150	Capsule	Yes (150 mg)	Approval based on bioequivalence of 150 mg tablet to TriCor® (160 mg micronized tablet); give with meals
TriCor®	NDA 21,656 (5 Nov 04)	48, 145	Tablet (NanoCrystal®)	Yes (145 mg)	Approval based on bioequivalence of 3×48 mg and 1×145 mg (fed) and TriCor® (200 mg micronized capsule); administer with or without food
Antara™	NDA 21,695 (30 Nov 04)	43, 87, 130	Capsule (micronized)	Yes (130 mg)	Approval based on bioequivalence of 130 mg (low-fat meal) and TriCor® (200 mg micronized capsule); give with meals
Fenoglide™	NDA 22-118 (10 Aug 07)	40, 120	Tablets	No	Summary Basis of Approval documents are not yet available; take with food to increase absorption (label in PLR format approved 29 February 2008)
Trilipix	NDA 22-224 (15 Dec 08)	45, 135	Capsules (Delayed Release)		Summary Basis of Approval documents are not yet available

Source: Mutual NDA 22-418.

**Appendix B-Mutual Response to DSI Citation/ Clinical Request**

3 June 2009

Mary Parks, M.D., Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Building W022  
Silver Spring, MD 20993

**Re: NDA 22-418  
Fenofibric Acid Tablets, 35 mg and 105 mg  
Sequence No. 0010: Response to 21 May 2009 Request  
for Information**

Dear Dr. Parks:

Please refer to **NDA 22-418 for Fibricor™** (fenofibric acid), submitted 15 August 2008 and a request for information sent by Kati Johnson in an e-mail on 21 May 2009. The request pertained to study MPC-028-07-1007 which demonstrated the bioequivalence of the proposed new drug product, fenofibric acid 105 mg, and the reference listed drug, TriCor® (fenofibrate) 145 mg, when each was administered as a single dose under standard fasting conditions. The request is stated below in bold, verbatim:

**According to the Division of Scientific Investigations, for study MPC-028-07-1007 the PRACS Institute-Cetero Research changed 50 of the 54 subjects' case report forms (CRFs) from meeting inclusion/exclusion criteria to not meeting inclusion/ exclusion criteria for medical history, physical examinations, clinical laboratory test results, vital sign measurements and ECG parameters 8 months after the completion of the study. The data from these 50 patients were included in the final study report.**

**Please provide the following to address this citing:**

- tabulation of all deviations**
- justification as to why patient data should be accepted.**

Mutual Pharmaceutical Company, Inc. (Mutual) has reviewed the deviations and in doing so, has identified that the study report (Section 10.2 and Appendix 16.2.2) identified only 49 subjects of the 50 subjects with laboratory deviations. This response discusses all 50 subjects with laboratory deviations.

As background, PRACS Institute-Cetero Research (PRACS) directly transcribed the inclusion and exclusion criteria in the protocol to the Eligibility Checklist case report form. The inclusion criterion that accounted for the protocol deviation affecting the 50 subjects noted above was stated as follows:

**“Medically healthy on the basis of medical history, physical examination, clinical laboratory test results (especially tests for renal and hepatic function) within the normal range, and no clinically significant vital sign measurements and ECG parameters, as deemed by the Medical Investigator.”**

During the conduct of the study, the clinical staff and Medical Investigator interpreted the above inclusion criterion as allowing the Medical Investigator to exercise clinical judgment as to the significance of any abnormality, including clinical laboratory test results. None of the values outside laboratory reference range were judged by the Medical Investigator as clinically significant and few warranted repeat. Thus, subjects with values outside reference range were enrolled as medically healthy with non-clinically significant laboratory values.

It was Mutual’s intent that the phrase “as deemed by the Medical Investigator” applied only to the vital sign and ECG measurements. Therefore, laboratory deviations would need to be approved by Mutual. As Mutual was not consulted and, thus, did not approve these protocol deviations, the subjects with results outside laboratory reference range were identified in the clinical study report, as having violated the protocol. During study report preparation, these deviations were reviewed and it was concluded that these laboratory deviations did not affect the pharmacokinetics of fenofibric acid.

A total of 50 of the 54 subjects enrolled in study MPC-028-07-1007 was identified with one or more pre-treatment laboratory values outside the laboratory reference range. The majority of these laboratory values pertained to abnormalities in serum chemistry (elevated CPK or low total protein), urinalysis (primarily blood and/or white cells in the urine of women), and % white cell differentials outside the laboratory normal range.

Mutual has re-reviewed these laboratory results and concurs with the Medical Investigator’s judgment. The subjects were healthy and the deviations were minor with no hepatic or renal dysfunction. None of the laboratory deviations presented a safety hazard and would not be expected to affect the pharmacokinetics of fenofibric acid.

A summary of the deviations and justification as to why the data should be accepted is provided in the **Attachment**. A listing of all clinical laboratory deviations at screening and check-in, organized by subject, is provided in **Appendix 1**. Should any additional tabulation be needed, Mutual will provide to the Division upon request.

The electronic files submitted for this application have been scanned for viruses with AVG Antivirus, using virus definitions of 3 June 2009. Please do not hesitate to contact me with any questions. I can be reached by telephone at (215) 288-6500 / (800) 523-3684.

Sincerely,

*Dr. Mary Parks*  
*3 June 2009*

*Page 24*

Robert Dettery  
Vice President, Regulatory Affairs  
Mutual Pharmaceutical Company, Inc.

**ATTACHMENT**

**Response to 21 May 2009 Request for Information**

## RESPONSE TO 21 MAY 2009 REQUEST FOR INFORMATION

The FDA request dated 21 May 2009 is stated in bold verbatim below:

**According to the Division of Scientific Investigations, for study MPC-028-07-1007 the PRACS Institute-Cetero Research changed 50 of the 54 subjects' case report forms (CRFs) from meeting inclusion/exclusion criteria to not meeting inclusion/exclusion criteria for medical history, physical examinations, clinical laboratory test results, vital sign measurements and ECG parameters 8 months after the completion of the study. The data from these 50 patients were included in the final study report.**

**Please provide the following to address this citing:**

**-tabulation of all deviations**

**-justification as to why patient data should be accepted**

### MUTUAL PHARMACEUTICAL COMPANY, INC. RESPONSE

#### **Background Information**

PRACS Institute-Cetero Research (PRACS) conducted MPC-028-07-1007 for Mutual Pharmaceutical Company, Inc. (Mutual). As part of their procedure, they directly transcribed the inclusion and exclusion criteria in the protocol to an Eligibility Checklist case report form.

The inclusion criterion that accounted for the protocol deviation affecting the 50 subjects noted above was stated as follows:

**“Medically healthy on the basis of medical history, physical examination, clinical laboratory test results (especially tests for renal and hepatic function) within the normal range, and no clinically significant vital sign measurements and ECG parameters, as deemed by the Medical Investigator.”**

During the conduct of the study, the clinical staff and Medical Investigator interpreted the above inclusion criterion as allowing the Medical Investigator to exercise clinical judgment as to the significance of any abnormality, including clinical laboratory test results. None of the values outside laboratory reference range were judged by the Medical Investigator as clinically significant and few warranted repeat. Thus, subjects with values outside reference range were enrolled as medically healthy with non-clinically significant laboratory values.

**It had been the Mutual's intent that the phrase “as deemed by the Medical Investigator” applied only to the vital sign and ECG measurements. Therefore, laboratory deviations would need to be approved by Mutual. As Mutual was not consulted and thus, did not**

approve these protocol deviations, the subjects with results outside laboratory reference range were identified in the clinical study report as having violated the protocol. During study report preparation, these laboratory deviations were reviewed and it was concluded that they did not affect the pharmacokinetics of fenofibric acid.

A total of 50 of the 54 subjects enrolled in study MPC-028-07-1007 was identified with one or more pre-treatment laboratory value outside laboratory reference range. The majority of these laboratory values pertained to abnormalities in serum chemistry (elevated CPK or low total protein), urinalysis (primarily blood and/or white cells in the urine of women), and % white cell differentials outside laboratory normal range.

**In response to FDA's request, an overview of the protocol-stipulated laboratory tests performed for Study MPC-028-07-1007 is provided in Section 1. Deviations from protocol-stipulated laboratory values are discussed in Section 2. A summary of deviations on laboratory tests that were not required by protocol is provided in Section 3. A justification as to why the data should be accepted is presented in Section 4.**

A listing of all clinical laboratory deviations at screening and check-in, organized by subject, is provided in **Appendix 1**.

1. **PROTOCOL STIPULATED LABORATORY TESTS FOR STUDY MPC-028-07-1007**

Protocol MPC-028-07-1007 stipulated that the following laboratory tests were to be performed at screening and check-in.

- Blood chemistry (after at least an 8-hour fast at screening): blood urea nitrogen (BUN), creatinine, glucose, total bilirubin, aspartate transaminase (AST/SGOT), alanine transaminase (ALT/SGPT), alkaline phosphatase, albumin, total protein and creatine phosphokinase (CK)
- Blood chemistry (at check-in): blood urea nitrogen (BUN), creatinine, total bilirubin, aspartate transaminase (AST/SGOT), alanine transaminase (ALT/SGPT), and creatine phosphokinase (CK)
- Urinalysis by dipstick: specific gravity, blood, bilirubin, glucose, ketones, leukocyte esterase, nitrite, pH, protein, and urobilinogen (microscopic analysis in the event of abnormalities)
- White blood cell (WBC) count, differential, and platelet count
- Red blood cell (RBC) count, hemoglobin, and hematocrit

Deviations from the protocol-stipulated laboratory parameters are discussed in **Section 2**.

A number of subjects also had laboratory test results as part of screening for another study. These were taken into consideration by the Medical Investigator even though the tests were not required for Study MPC-028-07-1007. These tests included: cholesterol, red cell indices (MCH, MCHC, MCV, and RDW) and mean platelet volume (MPV). Deviations from these additional laboratory parameters that were not required by Protocol MPC-028-07-1007 are discussed in **Section 3**.

## 2. PROTOCOL STIPULATED LABORATORY DEVIATIONS

A total of 48 of the 54 subjects enrolled in MPC-028-07-1007 were identified with one or more pre-treatment laboratory value outside of the reference range. Ten of the subjects had values outside reference range only at screening, 8 subjects only at check-in, and 30 subjects at both screening and check-in. The remaining two subjects with laboratory deviations are discussed in **Section 3**.

The laboratory testing results are discussed below.

### 2.1. Serum Chemistry

A total of 30 subjects, 17 females and 13 males, had one or more abnormalities in serum chemistry test results prior to dosing. By protocol, tests of renal and hepatic function were singled out as needing to be within reference range. These parameters and CK, the only parameters that were to be repeated prior to dosing (upon check-in to the clinic) are discussed below. The only other laboratory parameter for which there were abnormalities prior to dosing is total protein, discussed last.

#### 2.1.1. Renal Function

One male subject (#17) had a BUN within the reference range at screening (16 mg/dL, reference range 6-22 mg/dL) and a value that was minimally above the upper limit at check-in (23 mg/dL); he had no other serum chemistry abnormality.

Another 18-year old male subject (#47) had a minimally elevated serum creatinine, 1.5 mg/dL (reference range 0.6 – 1.4 mg/dL), upon check-in to the study unit. The screening serum creatinine was 1.1 mg/dL. Mutual calculated creatinine clearances based on these values. Estimated creatinine clearance ranged from 90.3 to 123.1 mL/minute, consistent with normal renal function. BUN at each time point was 12 mg/dL within normal limits.

**These minor deviations in the 2 subjects would impact neither renal function nor the pharmacokinetics of fenofibric acid.**

In addition, there were 3 female subjects (#3, 34, and 36) with BUN values outside reference range, however, these were all below the lower limit of the laboratory reference range and therefore not of clinical importance.

The abnormalities are summarized in the table below.

**Subjects with BUN values above Laboratory Reference**

Subject #	BUN (mg/dL) [Reference range 6 - 22]	
	Screening	Check-in
3	8	5*
34	5*	8
36	13	5*

\* Below lower limit of reference range

**2.1.2. Hepatic Function**

There were 2 subjects (#10 and 19) with transaminases above laboratory reference limits at screening. None of the values were more than two times the upper limit at screening and all were within the reference range limits at study check-in. Neither subject had any other laboratory abnormalities other than as noted below. The transaminase abnormalities were as follows:

**Subjects with Transaminase Values above Laboratory Reference**

Subject #	ALT (IU/L) [Reference range 0 – 40]		AST (IU/L) [Reference range 0 – 42]	
	Screening	Check-in	Screening	Check-in
10	62*	30	53*	38
19**	29	29	47*	34

\* Above upper limit of reference range

\*\* Subject also had elevations in CK

Seven subjects, 5 males and 2 females had elevated total bilirubin values at one or both pre-dose time points. Of these, one subject (#37), a 21-year old female, had elevated values at both time points. Her other clinical laboratory test results (including hepatic transaminases) were normal and she had no abnormalities noted either by medical history or physical examination.

**Subjects with Total Bilirubin above Laboratory Reference**

Subject #	Total Bilirubin (mg/dL) [Reference range 0.2 - 1.2]	
	Screening	Check-in
6	1.0	1.3*
25	1.6*	1.1
28	1.4*	0.9
37	1.8*	1.6*
40	0.9	1.4*
42	2.1*	0.9
48	1.4*	1.0

\* Above upper limit of reference range

It is noted that 1 female subject (#31) had an alkaline phosphatase value below the lower limit of the laboratory reference range (28 IU/L, reference range 30 – 125 IU/L) at screening. This is not of clinical importance.

**These deviations would impact neither hepatic function nor the pharmacokinetics of fenofibric acid.**

### 2.1.3. Creatine Phosphokinase

Eleven subjects, 3 female and 9 male, had elevations in CK prior to treatment. In one of these subjects (Subject #7) the check-in value was within reference range and in 4 subjects (#19, 21, 47, and 48) the value was decreasing although still elevated. Of the abnormalities still present at check-in, 3 subjects (#8, 19, and 50) were more than twice the upper limit of the laboratory reference range. None of the subjects had any evidence of trauma or ischemic disease, renal failure, or other possible cause for the elevations. These were attributed to exercise in a young healthy population.

**Subjects with Elevations in Creatine Phosphokinase**

Subject #	Age (yrs) / Sex / Race	BMI	CK (IU/L) [Reference range 20 -200]	
			Screening	Check-in
7	21 / F / W	28.5	270*	65
8	30 / M / W	26.3	204*	462*
18	21 / M / W	22.9	159	242*
19	29 / M / W	29.4	1107*	433*
21	21 / M / A	23.4	554*	318*
32	28 / M / W	22.8	122	305*
43	21 / F / W	29.3	198	214*
44	20 / M / W	22.7	173	202*
47	18 / M / B	28.5	299*	213*
48	21 / M / W	26.2	555*	378*
50	27 / F / W	23.9	86	467*

\* Above upper limit of reference range

**These deviations would not impact the pharmacokinetics of fenofibric acid.**

### 2.1.4. Total Protein

Ten subjects, 9 female and 1 male, had total protein values slightly below the laboratory reference range, the only serum chemistry abnormality in 8 of the subjects. The values ranged from 6.0 to 6.3 g/dL (reference range 6.4 – 8.3 g/dL). There were no abnormalities in albumin.

**Subjects with Total Protein outside Reference Range**

Subject #	Total Protein (g/dL) [Reference range 6.4 – 8.3]
	Screening
16	6.0*
20	6.2*
23	6.3*
25	6.2*
31	6.3*
38	6.3*
40	6.3*
45	6.2*
49	6.3*
54	6.2*

\* Below lower limit of reference range

**These minor deviations would not impact the pharmacokinetics of fenofibric acid.**

**2.2. Urinalysis**

Urinalysis by dipstick was performed at screening and check-in for all 54 subjects. Microscopy (casts, WBC, RBC, bacteria, and crystals) was performed in response to any abnormality on the dipstick.

A total of 30 subjects, 23 female and 7 male, had abnormal urinalysis, 14 (12 female and 2 male) at check-in. None had evidence of any renal disease or infection. In 5 of the subjects, abnormalities of urinalysis were the only pre-treatment abnormalities (subject # 24, 27, 33, 52, and 53).

**2.2.1. Specific Gravity**

Specific gravity was below the lower limit of the laboratory reference range in 9 subjects and above the upper limit in 2 subjects. No subject was outside reference range at both screening and check-in.

**Subjects with Specific Gravity outside Reference Range**

Subject #	Specific Gravity – Dipstick [Reference range 1.005 – 1.030]	
	Screening	Check-in
26	1.020	1.003*
29	1.005	1.004*
30	1.003*	1.025
31	1.018	1.046*
34	1.002*	1.015
39	1.002*	1.025
42	1.025	1.004*
43	1.004*	1.025
45	1.020	1.004*
51	1.032*	1.010
52	1.010	1.004*

\*Outside reference range

The urine specific gravity abnormalities would not impact the pharmacokinetics of fenofibric acid.

**2.2.2. Crystals**

Six subjects had crystals, 4 of which were observed in urine samples obtained at check-in. The abnormalities that resulted in the performance of the microscopy are included in the summary table below.

**Subjects with Crystals in Urine**

Subject #	Reason for Microscopy		Crystals – Microscopy [Negative]	
	Screening	Check-in	Screening	Check-in
4	Leukocytes	Not done	Present	Not Done
13	Leukocytes	Leukocytes	None	Present
14	Blood	Blood	None	Present
33	Not done	Protein	Not done	Present
40	Protein	Not done	Present*	Not Done
49	Not done	Protein	Not done	Present

\* None on repeat 3 days later

These minor deviations would not impact the pharmacokinetics of fenofibric acid.

### 2.2.3. Protein

Five subjects had trace to 2+ protein in the urine.

#### Subjects with Protein / Casts in Urine

Subject #	Protein - Dipstick [Negative]		Casts - Microscopy [None]	
	Screening	Check-in	Screening	Check-in
25	1+	2+	None	None
33	Negative	1+	Not done	Present
40	Trace*	Negative	None	Not Done
42	Trace	Negative	None	Not Done
49	Negative	1+	Not done	None

\* None present upon repeat 3 days later

These minor deviations would not impact the pharmacokinetics of fenofibric acid.

### 2.2.4. Blood and/or RBCs in Urine

Eleven female subjects had blood in the urine as the only abnormality of urinalysis. Only trace amounts were present in two of the female subjects upon check-in to the unit.

#### Women with Blood / RBCs in Urine

Subject #	Blood - Dipstick [Negative]		RBCs - Microscopy [reference 0 - 2]	
	Screening	Check-in	Screening	Check-in
3	Negative	Negative	2-5*	Not done
9	1+	Negative	0-2	Not done
14	3+	Trace	2-5	5-10
23	3+	Negative	20-50	Not done
24	Trace	Negative	0-1	Not done
27	Trace	Negative	0-2	Not done
29	Trace	Negative	0-2	Not done
30	Trace	Negative	0-2	Not done
36	1+	Trace	0-2	None
37	2+	Negative	2-5	Not done
45	Trace	Negative	0-1	Not done

\* Microscopy performed due to nitrites in urine

Three male subjects had trace to 1+ blood in the urine at screening. In only one of the subjects were RBCs observed on microscopy. All three subjects had negative urine dipsticks for blood (or any other urinary abnormalities) at check-in.

**Men with Blood / RBCs in Urine**

Subject #	Blood - Dipstick [Negative]		RBCs - Microscopy [Reference 0 – 2]	
	Screening	Check-in	Screening	Check-in
39	1+	Negative	None	Not Done
47	Trace	Negative	None	Not Done
48	Trace	Negative	0-1	Not Done

These minor deviations in the presence of normal renal function would not impact the pharmacokinetics of fenofibric acid.

**2.2.5. Bacteria and/or White Cells in Urine**

A total of 7 female subjects had leukocytes, WBCs, and/or bacteria in their urine (none with abnormalities in WBC count). Three female subjects had leukocytes by dipstick at screening and/or check-in. In the remaining subjects, the observations were by microscopy performed due to other abnormalities. No urine cultures were performed.

**Women with Bacteria and/or Leukocytes / WBCs in Urine**

Subject #	Dipstick		Microscopy			
	Leukocytes [Negative]		WBCs [0 – 5]		Bacteria [None]	
	Screening	Check-in	Screening	Check-in	Screening	Check-in
3	Negative	Negative	10-20*	Not done	Many*	Not done
4	1+	Negative	None	Not done	Rare	Not done
13	Trace	Trace	0-2	5-10	None	Few
14	Negative	Negative	None**	0-2**	Moderate**	Few**
25	Negative	Negative	2-5***	2-5**	Many***	Many***
30	Negative	Negative	None**	Not done	Moderate**	Not done
36	Negative	Trace	0-2**	2-5	Few**	Few

\*Microscopy done due to positive nitrites in the urine at screening  
 \*\* Microscopy done due to blood in urine (and, for #30, due to low specific gravity)  
 \*\*\* Microscopy done due to protein in urine

One male subject, with no evidence of leukocytes by dipstick, had significant numbers of WBCs by microscopy. These were confirmed by repeat testing. The only other observation was rare bacteria. Results were negative at check-in.

**Men with Bacteria and/or Leukocytes / WBCs in Urine**

Subject #	Dipstick		Microscopy			
	Leukocytes [Negative]		WBCs [0 – 5]		Bacteria [None]	
	Screening	Check-in	Screening	Check-in	Screening	Check-in
40	Negative	Negative	20-50*	Not done	Rare*	Not done

\* Microscopy done due to trace protein in urine; upon repeat 3 days later, 20-50 WBCs and “few” bacteria

These minor deviations in the presence of normal renal function would not impact the pharmacokinetics of fenofibric acid.

### 2.2.6. Ketones

Six subjects had ketones in the urine. In 4 of the 6 subjects, results were negative at check-in to the study unit.

**Subjects with Ketones in Urine**

Subject #	Ketones – Dipstick [Negative]	
	Screening	Check-in
9	2+	Negative
22	Trace	Negative
30	Negative	2+
46	Trace	1+
51	1+	Negative
53	Trace	Negative

These deviations would neither impact renal function nor the pharmacokinetics of fenofibric acid.

### 2.3. White Blood Cell Count and Differential

A total of 25 subjects (14 female and 11 male) had one or more pre-treatment value outside laboratory reference range. The abnormalities are categorized below. The values were minimally outside reference range, none determined to be clinically significant by the medical investigator. None of the subjects had any abnormality evident at initial examination that would explain or be a result of these abnormalities.

#### 2.3.1. Elevations in WBC Count and/or Neutrophils

Four subjects (#16, 44, 46, and 51) had WBC counts, absolute neutrophils or % neutrophil counts that were above laboratory reference range. Repeat testing in one subject (#44) showed that the absolute neutrophil count was lower, although still outside the reference range. Counts in the other 3 subjects were within reference range.

**Subjects with WBC and/or Neutrophils Counts  
Above Laboratory Reference**

Subject #	WBC Count [4.5 – 11.0 × 10 <sup>3</sup> /μL]		Neutrophil Count (%) [2.3 – 7.7 × 10 <sup>3</sup> /μL]	
	Screening	Check-in	Screening	Check-in
16	6.9	11.9*	4.3 (62.1%)	8.5 (71.6%)*
44	14.4*	10.1	11.8 (82.1%)*	7.9 (78.7%)*
46	12.1*	10.6	9.4 (77.1%)*	7.1 (66.8%)
51	11.8*	10.5	8.1 (68.8%)*	6.3 (60.0%)

\* Above upper limit of reference range

An additional 9 subjects had % neutrophils above laboratory reference, identified in the table below (with the total WBC count remaining within reference range). Six of these

subjects also had low % lymphocytes; none had absolute lymphocyte counts outside the reference range ( $0.8 - 5.0 \times 10^3/\mu\text{L}$ ).

**Subjects with % Neutrophils and % Lymphocytes  
Outside Laboratory Reference Range**

Subject #	Neutrophil Count (%) (50.0 - 70.0%)		Lymphocyte Count (%) (18.0 - 45.0%)	
	Screening	Check-in	Screening	Check-in
3	3.6 (61.0%)*	7.4 (76.4%)*	1.8 (30.5%)	1.6 (16.8%)*
6	7.6 (79.3%)*	4.4 (61.6%)	1.1 (11.0%)*	1.7 (23.7%)
13	3.7 (60.7%)	7.3 (76.0%)*	1.8 (30.4%)	1.8 (18.7%)
26	6.8 (75.2%)*	6.9 (72.5%)*	1.8 (19.7%)	2.2 (22.7%)
30	5.1 (70.1%)*	5.1 (65.6%)	1.8 (24.9%)	2.3 (23.9%)
35	3.7 (69.6%)	4.6 (75.3%)*	1.0 (18.5%)	1.0 (17.1%)*
42	5.9 (76.6%)*	5.8 (71.6%)*	1.3 (16.8%)*	1.7 (20.5%)
43	4.7 (67.3%)*	6.6 (73.7%)*	1.6 (23.2%)	1.6 (17.9%)*
45	4.8 (69.0%)	7.9 (78.2%)*	1.4 (20.2%)	1.7 (17.1%)*

\* Outside reference range

**2.3.2. Low WBC Count and/or Neutrophils**

Two subjects (#22 and 28) had a low WBC count and one subject (#10) had a low absolute neutrophil count (with normal WBC count).

Three additional subjects had low % neutrophils (#25, #29, and #41) at either screening or check-in, without abnormalities in WBC or neutrophil count. These values ranged from 48.2 to 49.5% (reference range 50.0 - 70.0%).

**Subjects with WBC and/or Neutrophil Counts  
Below Laboratory Reference**

Subject #	WBC Count [ $4.5 - 11.0 \times 10^3/\mu\text{L}$ ]		Neutrophil Count (%) [ $2.3 - 7.7 \times 10^3/\mu\text{L}$ ]	
	Screening	Check-in	Screening	Check-in
10	5.9	9.2	2.0 (34.2%)*	6.4 (69.1%)
22	4.3*	6.7	2.6 (60.0%)	4.7 (70.1%)
28	4.6	4.3*	2.5 (54.1%)	2.5 (59.2%)

\*Outside reference range

**2.3.3. Eosinophils**

A total of 7 subjects, listed in the table below, had elevated % eosinophils, ranging from 4.4 to 6.0% (reference range 0.0 - 4.0%). Four subjects (#17, 28, 31, and 47) had elevated % eosinophils as their only pre-treatment WBC-related abnormality. No subject had an absolute eosinophil count above the upper limit of reference ( $0.4 \times 10^3/\mu\text{L}$ ).

**Subjects with % Eosinophils above Laboratory Reference Range**

Subject #	WBC Count [4.5 – 11.0 × 10 <sup>3</sup> /μL]		% Eosinophils [0.0 – 4.0%]	
	Screening	Check-in	Screening	Check-in
17	4.9	5.6	3.4%	5.1%*
18	6.2	5.8	4.0%	5.1%*
28	4.6	4.3*	5.7%*	3.2%
29	5.9	5.5	3.0%	4.4%*
31	5.1	5.8	6.0%*	3.0%
40	7.2	6.6	2.5%	5.2%*
47	4.9	5.8	5.1%*	4.6%*

\* Outside reference range

**2.3.4. Miscellaneous**

Five subjects had % monocytes minimally above the upper limit of normal. In 2 subjects (#7 and #9) these were the only hematology abnormalities. One subject (#40) also had % basophils above normal.

**Subjects with % Monocytes and/or % Basophils  
above Laboratory Reference Range**

Subject #	Cell Type	Reference Range	Screening	Check-in
6	Monocytes	0.0 – 10.0%	8.3%	10.4%*
7	Monocytes	0.0 – 10.0%	9.8%	11.0%*
9	Monocytes	0.0 – 10.0%	12.4%*	10.2%*
10	Monocytes	0.0 – 10.0%	11.1%*	4.4%
40	Monocytes	0.0 – 10.0%	10.2%*	12.2%*
	Basophils	0.0 – 1.0%	1.8%*	1.4%*

\* Outside reference range

**2.4. Red Blood Cell Indices**

Four subjects (#11, 14, 25, and 52) were screened with hemoglobin values below 12 g/dL, the protocol inclusion criterion; all were enrolled by protocol exception and in three, the check-in value was 12.0 g/dL. These subjects are not discussed further because the hemoglobin values were within the normal range.

**2.4.1. Decreased RBCs**

Two subjects, 1 female (#46) and 1 male (#39), had RBC counts below laboratory reference prior to dosing. The male subject also had low hemoglobin and hematocrit values.

**Subjects with RBC Indices below Laboratory Reference Range**

<b>Women</b>						
	Screening	Check-in	Screening	Check-in	Screening	Check-in
Subject #	RBC Count [3.80 – 5.20 × 10 <sup>3</sup> /μL]		Hemoglobin [11.5 – 15.5 g/dL]		Hematocrit [33.0 – 45.0%]	
46	3.97	3.74*	12.6	12.0	36.2	34.6
<b>Men</b>						
Subject #	RBC Count [4.34 – 6.00 × 10 <sup>3</sup> /μL]		Hemoglobin [13.5 – 17.5 g/dL]		Hematocrit [40.0 – 50.0%]	
39	4.31*	3.98*	13.6	12.9*	38.6*	36.2*

\* Outside reference range

**2.4.2. Elevated RBCs**

Three subjects, 2 female (# 4 and 14) and 1 male (#6), had RBC-related parameters that were above reference range. These are summarized below.

**Subjects with RBC Indices above Laboratory Reference Range**

<b>Women</b>						
	RBC Count [3.80 – 5.20 × 10 <sup>3</sup> /μL]		Hemoglobin [11.5 – 15.5 g/dL]		Hematocrit [33.0 – 45.0%]	
Subject #	Screening	Check-in	Screening	Check-in	Screening	Check-in
4	5.32*	5.75*	15.1	16.6*	45.1*	48.8*
14	5.67*	5.80*	11.8	12.0	37.0	38.4
<b>Men</b>						
Subject #	RBC Count [4.34 – 6.00 × 10 <sup>3</sup> /μL]		Hemoglobin [13.5 – 17.5 g/dL]		Hematocrit [40.0 – 50.0%]	
6	5.33	5.42	17.5	17.9*	50.5*	51.6*

\*Outside reference limit

**These minor deviations would not impact the pharmacokinetics of fenofibric acid.**

3. **SUMMARY OF DEVIATIONS ON LABORATORY TESTS NOT REQUIRED BY PROTOCOL MPC-028-07-1007**

A number of subjects had laboratory tests performed that were not required per protocol MPC-028-07-1007. Five subjects (# 5, 11, 14, 28, and 34) were outside the laboratory range. Three of these subjects (#14, 28, and 34) have been discussed in **Section 2**.

The remaining two subjects (#5 and #11) are discussed below.

Subject #5, a 22-year old woman, had a low mean platelet volume at screening (6.9 fL, reference range 7.0 – 12.0 fL). The value was within reference range at check-in (7.0 fL). She had no other laboratory values outside reference range.

Subject #11, a 22-year old woman, had MCH, MCV and RDW values outside laboratory normal range at screening and check-in, as summarized in the table below.

**Subjects with RBC Indices outside Laboratory Reference Range**

Subject #	Screening	Check-in	Screening	Check-in	Screening	Check-in
	RDW [11.5 – 14.5%]		MCH [26.0 – 34.0 pg]		MCV [80.0 – 100.0 fL]	
11	15.1*	14.9*	25.4*	25.2*	76.6*	75.9*

\* Outside reference range

**These deviations would not impact the pharmacokinetics of fenofibric acid.**

4. **JUSTIFICATION AS TO WHY DATA SHOULD BE ACCEPTED**

A total of 50 of the 54 subjects enrolled in study MPC-028-07-1007 was identified with one or more pre-treatment laboratory value outside laboratory reference range. The majority of these laboratory values pertained to abnormalities in serum chemistry (elevated CPK or low total protein), urinalysis (primarily blood and/or white cells in the urine of women), and % white cell differentials outside laboratory normal range.

During the conduct of the study, the clinical staff and Medical Investigator interpreted the above inclusion criterion as allowing the Medical Investigator to exercise clinical judgment as to the significance of any abnormality, including clinical laboratory test results. None of the values outside laboratory reference range were judged by the Medical Investigator as clinically significant and few warranted repeat. Thus, subjects with values outside reference range were enrolled as medically healthy with non-clinically significant laboratory values.

Mutual has re-reviewed these laboratory results and concurs with the Medical Investigator's judgment. The subjects were healthy and the deviations were minor with no hepatic or renal dysfunction. None of the laboratory deviations presented a safety hazard and would not be expected to affect the pharmacokinetics of fenofibric acid.

*Dr. Mary Parks*  
*3 June 2009*

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/s/

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Iffat N Chowdhury  
6/9/2009 04:10:18 PM  
MEDICAL OFFICER

Eric Colman  
6/10/2009 11:02:35 AM  
MEDICAL OFFICER

10/16/08

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-418

Applicant: Mutual  
Pharmaceutical Company,  
Inc.

Stamp Date: August 15, 2008

Proposed Drug Name: Fibracor NDA/BLA Type: 505(b)(2)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			As this is a 505b2 application (RLD Tricor), the clinical section is limited to the safety of the submitted clinical pharmacology studies
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Submitted as Safety Summary (non-pooled safety data from 10 Mutual-sponsored PK studies, review of the FDA and WHO pharmacovigilance databases, published literature, and label from Tricor)
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			No efficacy studies were conducted
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			This is a 505b2, RLD is Tricor
<b>DOSE</b>					

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908



## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?		X		Not found by this reviewer in Modules 2 or 5
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?		X		Not found by this reviewer in Modules 2 or 5
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Yes, from a clinical standpoint, otherwise defer to other disciplines
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Requested waiver
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	Studies conducted in the U.S.
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	Data to be reviewed by clinical pharmacology
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			Submitted in Module 5

<sup>2</sup> The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Not found by this reviewer in Modules 1 or 2

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?** Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Iffat N. Chowdhury, MD	10/9/08
Reviewing Medical Officer	Date
Eric Colman, MD	10/10/08
Clinical Team Leader	Date

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this page is the manifestation of the electronic signature.**  
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/s/

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Iffat N Chowdhury  
10/16/2008 03:48:10 PM  
MEDICAL OFFICER

Eric Colman  
10/16/2008 03:52:24 PM  
MEDICAL OFFICER