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A Bioequivalence Study of Two Finofibrate Tablet Formulations in Indian Healthy Subjects

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Abstract

Aim: To compare the bioavailability of two Finofibrate 145 mg tablet as test formulation and 145 mg tablet as reference formulation.

Method: Randomized, single dose, open-label, three-treatment, three-period, three-sequence, crossover design under fasting period with 9 days wash out period was evaluated in 18 subjects.

For the analysis of pharmacokinetic properties, the blood samples were drawn taken up to 72 hours after dosing. Plasma concentration of Finofibrate was determined using High performance liquid chromatography (HPLC) – mass spectrometry method. Pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were tested for bioequivalence after log-transformation of data and ratios of t_{max} were evaluated.

Result: The point estimates and 90% confidence intervals (CI) A *vs.* C for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, for Finofibrate were 62.84%, 85.03%, 86.34% respectively. The point estimates and 90% confidence intervals (CI) B *vs.* C for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, for Finofibrate were 82.89%, 95.87% and 96.63% respectively.

Conclusion: Based on clinical, pharmacokinetic and statistical data obtained from 18 healthy adult male human subjects under fasting conditions, it may be concluded that a single dose of test formulation of drug 'Finofibrate' 145 mg tablet manufactured by Wockhardt Limited, India does not meet bioequivalence criteria of 80.00% to 125% for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ when compared with reference formulation 145 mg Finofibrate® 'Tablet.

Introduction

A generic drug product is one that is therapeutically equivalent to an innovator or first version of the drug product approved by the Food and Drug administration (FDA) and designated as the reference listed drug (RLD). ANDA (Abbreviated new drug application) is submitted to the Office of Generic Drugs and includes supporting data for the review and approval of a generic drug product. For approval, a sponsor of an ANDA must have information to show that the proposed generic product is pharmaceutically equivalent and bioequivalent, and therefore, therapeutically equivalent to the RLD [1,2].

Disease Hyperlipidemia is presence of raised or abnormal levels of lipids and/or lipoproteins in the blood of human body. Lipid and lipoprotein abnormalities are extremely common in the general population, and are regarded as a highly modifiable risk factor for cardiovascular disease due to the influence of cholesterol, one of the most clinically relevant lipid substances, on atherosclerosis [3]. Finofibrate is an oral antihyperlipidemic agent. Finofibrate is a prodrug that is hydrolyzed to Fenofibric acid. It is most effective in treating lipid disorders associated with very high elevations of serum triglycerides and very low density lipoprotein (VLDL) [4].

There are many generic products of Finofibrate in India and it must also go through the bioequivalence study in order to assure the efficacy, safety, and quality. The present study was conducted to investigate the pharmacokinetics and bioavailability of two Finofibrate tablet formulations in order to prove bioequivalence between both formulations.

In this investigation, we report randomized, single dose, open-label, three-treatment, three-period, three-sequence, crossover Clinical study evaluating the bioequivalence of two new test formulation A and B of Finofibrate 145 mg Tablets (manufactured by Wockhardt Limited, India) and reference formulation 145 mg Tricor® Tablet (Produced by Abbott India Limited). In this investigation, we report randomized, single dose, open-label, three-treatment, three-period, three-sequence, crossover Clinical study evaluating the bioequivalence of two new test formulation of A and B of Finofibrate 145 mg Tablets (manufactured by manufactured by Wockhardt Limited, India) and reference formulation 145 mg Tricor® Tablet (C).

Methods

Study design

A randomized, single dose, open-label, three-treatment, three-period, three-sequence, crossover bioequivalence study on two new formulation A and B of Finofibrate 145 mg Tablets in 18 normal, adult, human subjects under fasting condition.

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Randomization in study because, it is a chance allocation of subject to different treatments, to avoid any bias in the study. The drug was administered to subjects once only in each period. Three treatments means, test drug 'A' and 'B' and reference drug 'C' (145 mg Tricor® tablet) was studied in investigation. Subjects were checked in to the facility three times separated by washout period. All the subjects will be randomly assigned with any of the given three treatment sequences i.e. "ABC" or "BCA" or "CAB". In Cross over study, after sufficient washout period those who had treatment 'A' in first period got 'B' in the next period and vice versa [5].

The studies were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice, and USFDA regulations. The protocol and informed consent form were reviewed and approved by the institutional review board (Independent Investigational Review Board Inc, Plantation, FL), and all subjects provided written informed consent before participating.

Subject

Healthy males between 18.0 and 45.0 years of age (inclusive), body weight not less than 50 kg, body mass index between 18.0 and 25.0 (inclusive), calculated as (weight in kg)/(height in m)^2 and no history of disease or clinically significant findings on physical or laboratory examination were eligible to participate. Having no significant disease or clinically significant abnormal laboratory values on laboratory evaluations, medical history or physical examination during screening. Subject must have normal 12 lead ECG, normal X-ray chest (Postero-anterior view), negative breath alcohol test and negative urine Screen for drugs of abuse viz Benzodiazepines, Cannabinoids, Amphetamines, Cocaines, barbiturates and Opiates.

Treatment

Total 18 normal, adult, human subjects were checked in the study. The subjects were given standardized dinner after that they underwent fasting overnight for 10 hours. Subjects were housed in the facility from at least 11 hours prior to dosing till 24.0 hours after dosing time in each period. Drug administration in first period was followed by a washout period 09 days before subjects are switched over to the other treatment in the second and third period depending on the randomization schedule.

Based on the randomization schedule, single dose of Finofibrate 145 mg tablet (either test or reference) ware administered along with 240 ml of water at room temperature in sitting posture in each period. The trained personnel were administered the dose as per the scheduled time, predetermined for each subject. The subjects were instructed not to chew or crush the tablet but to consume with specified quantity of water.

The subjects were dosed next morning with the investigational product (IP) in the study after they have maintained 10 hr fasting as per protocol. Dosing was done according to the randomization schedule. The randomization code for the dosing was generated by the statistician in whom the sequence of IP administration was mentioned ("ABC" or "BCA" or "CAB") in table 1. The subjects were dosed as per schedule (Table 2). The subjects were given the IP accordingly with required amount of water under the observation of senior Clinical research associates (CRA) and principal investigator. After dosing, dosing label was pasted in respective case report form (CRF). After dosing, the dosing CRF was verified and signed by Dosing supervisor.

This study was an open label study; the subjects and the Investigator were not blinded towards the identity of the study medications. However, analysts were blinded towards identity of study medication administered.

Subject No.	Sequence	Periods		
		Period I	Period II	Period III
01	ABC	A	B	C
02	BCA	B	C	A
03	BCA	B	C	A
04	ABC	A	B	C
05	CAB	C	A	B
06	CAB	C	A	B
07	BCA	B	C	A
08	CAB	C	A	B
09	BCA	B	C	A
10	ABC	A	B	C
11	ABC	A	B	C
12	CAB	C	A	B
13	BCA	B	C	A
14	CAB	C	A	B
15	BCA	B	C	A
16	ABC	A	B	C
17	ABC	A	B	C
18	CAB	C	A	B

Table 1: Individual Drug-Dose Information.

Time Relative to Dose Administration (H)	Vital Signs	Blood Sampling
-11.00	√	
Before –10.00		
-1.00 to 0.00	√	√
DOSING(00.00)		
0.5		√
1.0		√
1.5		√
2.0		√
2.5		√
3.0		√
3.33		√
3.66		√
4.0		√
4.5		√
5.0		√
6.0	√	√
8.0		√
10.0		√
11.0	√	
12.0		√
16.0		√
24.0	√	√
48.0 *		√
72.0**	√	√

√ Indicates study activities.
*Indicates samples will be collected on ambulatory basis.
**Medical examination will be done at the time of check in and at the end of the study (72.0 hr post dose sample of period III).

Table 2: Schematic representation of the study schedule for safety assessment and blood collection in period I/II/III.

Safety

Blood pressure, oral temperature, radial pulse and respiratory rate were measured at the time of check-in, prior to drug administration and approximately at around 4.0, 6.0, 11, 24, 48 and 72 hours post dose in each period. Subjects were asked for their well being at the time of vital signs measurements and the responses were recorded (Table 2).

To ensure the well being of the subject after the administration of IP, vital signs of the subjects were checked at regular intervals of time defined in the protocol [6].

All Adverse events, including both observed or volunteer's problems, complaints, signs or symptoms are recorded on the "Adverse Event Form" irrespective of its association with the administered drug product. Subjects were monitored throughout the study period for adverse events. Subjects will be instructed to bring to the notice of the nurse or the physician any discomfort that may occur during their stay at the clinical facility [6].

Medical examination including recording vital signs of the subjects was conducted at the end of the study. It also included laboratory analysis of blood samples for hematology, liver function and renal function tests. Post study laboratory parameters that are out of specified ranges are individually assessed and repeated if deemed necessary by the medically qualified reviewer. There were four adverse events were reported these were abnormal clinical laboratory values [6].

After the completion of the study the subjects were checked- out. In the check out process the subjects undergo a medical check up to ensure that they are healthy even after participating in the study. The study cycle was repeated after the washout period when the subjects were crossed over to other treatment [7].

Assessments

Pharmacokinetics: During each treatment period, a total of 20 venous blood samples will be collected from each subject as per the following schedule:

Predose (0.0 hr) and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.33, 3.66, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 48.0 and 72.0 hours (Table 2). Samples at 48.0 and 72.0 hours will be collected on ambulatory basis.

After collection of blood samples from all the subjects at each time point, the samples were centrifuged at 3000 ± 50 rotation per minute (RPM) for a period of 10 minutes at a temperature of 4 ± 3°C to separate the plasma. All such separated plasma samples were transferred to pre-labeled (Project no., Subject no., Period, Sampling time point and aliquot number) storage vials arranged in duplicate sets corresponding for each subject. The vials were stored upright at a temperature of -50°C or colder till the completion of analysis.

Shimadzu HPLC equipped with pump, auto sampler, mass spectrometer MDS SCIEX API 4000 LC/MS/MS and data equisition system (analyst software version 1.4.1) were used for the quantitative determination of analyte in human plasma. Plasma samples of subjects completing clinical phase was assayed for drug Finofibrate concentrations using a validated chromatographic method, which is in accordance with the international guidelines.

The analysis of subject's samples was done using a calibration curve with quality control samples, distributed throughout each batch.

Statistical analysis: Calculation of pharmacokinetic parameters was performed using the non-compartmental model of the pharmacokinetic software WinNonlin® 5.1. The statistical analysis for establishing bioequivalence was performed using the statistical package statistical analysis software (SAS®) 9.1 was used for the estimation of least square mean differences (Test-Reference) of the test and reference formulation on the log-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. Here C_{max} means maximum concentration and AUC means area under curve [8].

Results

Demographic result

All the 18 subjects admitted in to the study fulfilled the inclusion and exclusion criteria. All the subjects were of normal health based on general physical examination and laboratory test reports. None of the subject had any relevant or significant previous medical history that could affect the study results.

Pharmacokinetic results

Pharmacokinetic parameters such as C_{max}, T_{max} (Time at maximum concentration), Area under curve (AUC_{0-t}), AUC_Extrapoleted (%), K_{el} (First order rate constant associated with the terminal (log-linear) portion of the curve) and $t_{1/2}$ (Elimination half life) were calculated. 90% confidence intervals with least square geometric test to reference mean ratio formed the basis for pharmacokinetic and statistical conclusion of the test formulation. Intra subject variability, p-value from analysis of variance (ANOVA) and power values was also calculated.

All the pharmacokinetic parameters statistical values were calculated using LinMax procedures of WinNolin® Version 5.1 (Pharsight Corporation USA) software application and the SAS® system Version 9.1, respectively, at Clinical Pharmacokinetic and Biopharmaceutics Department of Wockhardt Ltd, India.

The tables (Tables 3 and 4) and figures (Figures 1 and 2) illustrate pharmacokinetic and statistical and mean graph obtained for Drug Finofibrate.

Pharmacokinetic analysis

Area under the plasma concentration time curve (AUC_{0-t}, t=72 hr) and $AUC_{0-\infty}$:

- **Parent drug AUC_{0-t}:** The AUC_{0-t} for test products A ranged from Mean ± standard deviations (S.D.) of 272.6656 ± 43.761 ng.h/ml and the AUC_{0-t} for test products B ranged from Mean ± SD of 289. 1733 ± 55.899 ng.h/ml. The AUC_{0-t} for reference product C ranged from 388.75 to 3244.16 ng.h/ml with a Mean ± SD of 256.8569 ± 83.2772 ng.h/ml.

The geometric values for the test products A, test products B and reference product C were found to be 131.30 ng.h/ml and145.48 ng h/ml and 165.75 ng h/ml respectively.

Parent drug $AUC_{0-\infty}$: The $AUC_{0-\infty}$ for test product A and test product B ranged from with a Mean ± SD of 323.9973 ± 54.629 ng.h/ml and 344.9106 ± 64.850 respectively. The $AUC_{0-\infty}$ for reference product C ranged from a Mean ± SD of 1305.2371 ± 56.110 ng.h/ml.

The geometric_values for the test products A and test products B and reference products C were found to be 131.30 ng.h/ml and 145.48 ng.h/ml and 165.75 ng.h/ml.

Elimination rate constant (K_{el}):

- **Parent drug:** The Mean ± SD values of the elimination rate constant (K_{el}) were found to be $0.0674 ± 0.011$ h^{-1} and $0.0969 ± 0.017$ h^{-1} for test product A and test products B respectively and $0.0688 ± 0.011$ h^{-1} for reference product C.

The geometric mean values for both the test products A and test products B and reference products C were found to be 0.04 h^{-1} and 0.04 h^{-1} and 0.04 h^{-1} respectively.

Elimination half-life ($t_{1/2}$):

- **Parent drug:** The Mean ± SD values of elimination half-life ($t_{1/2}$) were found to be $27.8189 ± 4.731$ h and $26.3192 ± 5.269$

Parameter	Drug Finofibrate		
	Test Product (A)	Test Product (B)	Reference Product(C)
C_{max} (ng/mL)			
Geometric	11.033 ± 1.855	16.310 ± 2.740	15.088 ± 1.720
Mean	6.34	8.31	11.18
CV%	28.02	31.71	15.22
N	18	18	18
T_{max} (hr)			
Median	4.50 ± 1.156	4.50 ± 0.822	5.00 ± 1.155
Geometric	2.91	2.75	2.50
Mean	2.56	2.74	2.48
CV%	44.11	28.81	42.65
N	18	18	18
AUC_{0-t} (ng.hr/mL)			
Geometric	272.6655 ± 43. 766	289.1733 ± 55.899	256.8569 ± 83.2762
Mean	120.10	134.05	153.56
CV%	34.91	38.82	27.77
N	18	18	18
$AUC_{0-∞}$ (ng.hr/mL)			
Geometric	323.9973 ± 54.6	344.9106 ± 64.850	305.2371 ± 56.110
Mean	131.30	145.48	165.75
CV%	39.45	41.30	32.23
N	18	18	18
AUC_Extrap ... (%)			
Geometric	15.92 ± 4.658	13.55 ± 3.535	15.85 ± 4.750
Mean	7.09	6.97	5.82
CV%	55.32	45.36	65.60
N	18	18	18
K_{el} (hr^{-1})			
Geometric	0.0674 ± 0.011	0.0969 ± 0.017	0.0688 ± 0.011
Mean	0.04	0.04	0.04
CV%	28.32	42.02	27.39
N	18	18	18
$T_{1/2}$ (hr)			
Median	27.8189 ± 4.731	26.3192 ± 5.269	28.0859 ± 4.896
Geometric	19.41	18.31	17.58
Mean	18.70	17.96	17.96
CV%	24.44	28.04	26.23
N	18	18	18

Table 3: Pharmacokinetic results calculated for Drug Finofibrate.

Parameter	$AUC_{0-∞}$ (ng..hr/mL)	C_{max} (ng/mL)	AUC_{0-t} (ng.hr/mL)
LSM Ratio:			
A/C (%)	56.96%	78.78%	79.69%
B/C(%)	75.56%	88.82%	89.19%
90% Confidence interval A vs.C			
Lower Limit	51.93%	72.99%	73.56%
Upper Limit	62.84%	85.03%	86.34%
90% Confidence interval B vs.C			
Lower Limit	68.88%	82.29%	82.32%
Upper Limit	82.89%	95.87%	96.63%
p-Values (ANOVA):			
A	1	0.6329	0.5321
B	0.8486	0.0136	0.0143
Intra-subject Variability:CV%			
(A/C)	15.35	12.64	13.27
(B/C)	15.35	12.64	13.27
Power (%):			
(A/C)	0.9884	0.9986	0.9974
(B/C)	0.9884	0.9986	0.9974

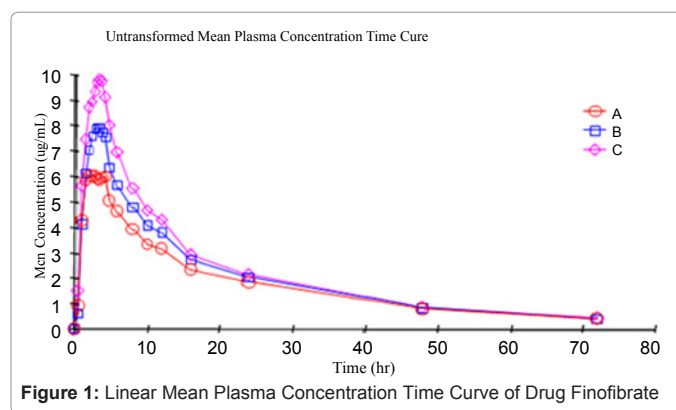**Table 4:** Summarized statistical values for Drug Finofibrate in 18 subjects.

Figure 1: Linear Mean Plasma Concentration Time Curve of Drug Finofibrate

for test product A and test products B and $28.0859 ± 4.896$ h for reference product C.

Parent drug: The Median half-life ($t_{1/2}$) values for the Test A and test products B and reference products C were found to be 19.4 h and 18.31 h and 17.58 h respectively.

Residual area (AUC_%Extrap_obs):

- **Parent drug:** The Mean ± SD values of the Residual Area (%) were found to be $15.92 ± 4.658$ and $13.55 ± 3.535$ for Test Product A and test products B and $15.85 ± 4.750$ for reference product C.

Statistical results

Geometric LSM ratio and 90% confidence interval: The test by reference geometric least square mean ratio and 90% confidence interval obtained for C_{max}, AUC_{0-t} and $AUC_{0-∞}$ were as follows:

- **Parent drug (A):** Least square mean (LSM) ratio C_{max} 56.96% and CI 51.96% to 62.84%, AUC_{0-t} LSM ratio 78.78% and Confidence interval (CI) 72.99% to 85.09% and $AUC_{0-∞}$ LSM ratio 79.69% and 73.56% to 86.34%, which shows all the values are not within the bioequivalence acceptance range 80.00% to 125.00%.

Figure 2: Semi log-transformed Mean Plasma Concentration Time Curve for Drug Finofibrate.
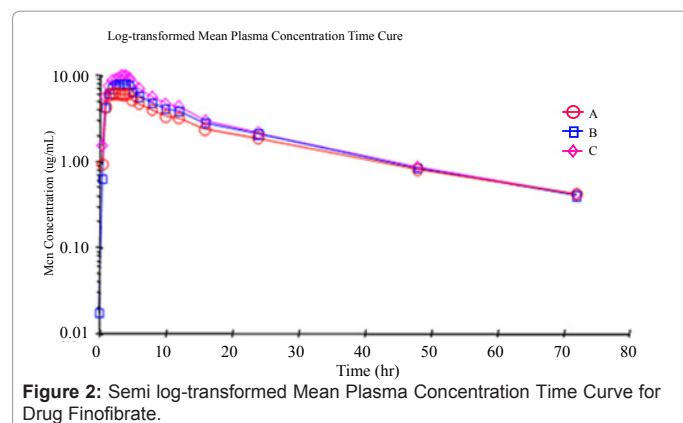
- **Parent drug (B):** LSM ratio C_{max} 75.56% and CI 68.88% to 82.89%, AUC_{0-t}, LSM ratio 88.82% and 82.29% to 95.87% and $AUC_{0-\infty}$ LSM ratio 89.19% and CI 82.32% to 96.63%, which shows all the values are not within the bioequivalence acceptance range 80.00% to 125.00%, only the upper limit of CI, AUC_{0-t}, $AUC_{0-\infty}$ of C_{max} exceeding.

p-values (ANOVA): The p-value should be greater than 0.05 for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for period and formulation effects. For sequence effect it should be greater than 0.01.

The p-values obtained from ANOVA for sequence effect of Drug '0015485' greater than 0.05 for C_{max} (1.0 and 0.8486), AUC_{0-t} (0.6329 and 0.0136) and $AUC_{0-\infty}$ (0.5321 and 0.0143) which indicates no statistically significant differences were observed for sequence effect on pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{o-\infty}$.

Intra-subject variability:

- **Parent drug (A):** The coefficients of variation (CV%) corresponding to intra-subject variability for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Drug '0015485' are 15.35%, 12.64%, 13.27% respectively which were found to be less than 30%.

- **Parent drug (B):** The coefficients of variation (CV%) corresponding to intra-subject variability for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for '0015485' are 15.35%, 12.64%, 13.27% respectively, which were found to be less than 30%.

Power:

- **Parent drug (A):** The power values obtained for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are 98.84%, 99.86%, 99.74% respectively, which were greater than 80.00% the desired power to support the bioequivalence test, and hence test, and hence considered to be adequate for supporting bioequivalence conclusions.

- **Parent drug (B):** The power values obtained for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are 98.84%, 99.86%, 99.74% respectively, which were greater than 80.00% the desired power to support the bioequivalence test, and hence test, and hence considered to be adequate for supporting bioequivalence conclusions.

Safety results: There was one adverse events reported which was mild fever Subject no. 11 adverse events was resolved, others two (Subject no. 08 and Subject no. 14) were withdrawn on their own accord. The adverse event was mild and unlikely to study medication

administered to the subjects. From the adverse event profile and tolerability of the subjects, it appeared that the test product was equally safe as that of reference product.

Discussion

Bioequivalence of different formulations of the same drug substance involves equivalence with respect to the rate and extent of absorption. Two formulations whose rate and extent of absorption differ by 20% to 25% or less are generally considered bioequivalent. Nearly 20% to 25% usage of drug rule is based on a medical decision that for most of the drugs, having approximately 20% to 25% difference in the concentrations of the active ingredient in blood will not be clinically significant. In order to verify the above criteria two sided statistical tests are generally carried out using log transformed data from bioequivalence study. One test is used, to verify that the average response for the generic product is not more than 20% below that for innovators product and the other test is used to verify that the average response for generic product is not more than 25% of innovators product. This test is carried out using 0.05 level of significance.

For approval of ANDA (Abbreviated new drug application), the generic company must show that a 90% confidence interval for that ratio of the mean response of its product to that of innovator is within the limits of 0.8 and l.25 using log transformed data. If the true average response of the generic product is below 20% and above 25% the innovator product's average, one or both the confidence limits are likely to fall out side the acceptable range and the product will fail the bioequivalence test.

Any reason may cause failure of any Bioequivalence study from the stage of formulation development to stastical bioanalytical process results. There are high chances of failure of bioequivalence study because of actual difference found in test product and reference product formulation. In the clinical phase of Bioequivalence study the reasons may be inadequate based on inclusion and exclusion criteria, non-compliance with study protocol and inappropriate blood sample collection time points. It is very essential to select uniform population for the study. If there is more inter subject variability then chances for failure of Bioequivalence test is more through inappropriate method development, errors during sample processing and analysis, wrong sample size calculation, wrongly applied statistical analysis methods etc.

The available literature on Bioequivalence studies on drug Finofibrate shows the drug Finofibrate is well tolerated and shows greater antihyperlipidemic effectiveness and better compliance than other formulation of drug Finofibrate and other antihyperlipidemic along with simplified dosing regimen.

In the present bioequivalence study conducted on 18 healthy adult human subjects for the drug Finofibrate, is following acceptable limits for the criterion AUC_{o-t}, $AUC_{0-\infty}$ and C_{max}.

The results generated with reference formulation Tricor® indicates the reference drug values are in the acceptable limits for the criteria AUC_{o-t}, $AUC_{0-\infty}$ and C_{max}. In comparison the results of the study with test formulation of 145 mg Finofibrate and 145 mg Tricor® tablet thus lead to suggest that these two formulations are said to be bioinequivalent.

Conclusions

Based on clinical, pharmacokinetic and statistical data obtained

from 18 healthy adult male human subjects under fasting conditions, it may be concluded that a single dose of test formulation of drug 'Finofibrate' 145 mg tablet manufactured by Wockhardt Limited, India does not meet bioequivalence criteria of 80.00% to 125% for C_{max}, $AUC_{o\text{-}t}$ and $AUC_{0\text{-}\infty}$ when compared with reference formulation 145 mg Tricor® Tablet.

Acknowledgments

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