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# Bioavailability and Bioequivalence study of Finofibrate in healthy human volunteers

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## INTRODUCTION

Bioavailability means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action and bioequivalence stated as absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study (1).

Studies to measure Bioavailability (BA) and/or establish Bioequivalence (BE) of a product are important elements in support of Investigational new drug (INDs), new drug application (NDAs), abbreviated new drug application (ANDAs) and their supplements. As part of INDs and ANDAs for orally administered drug products, BA studies focus on determining the process by which a drug is released from the oral dosage form and moves to the site of action. BA data provide an estimate of the fraction of the drug absorbed, as well as its subsequent distribution and elimination. BA can be generally documented by a systemic exposure profile obtained by measuring drug and/or metabolite concentration in the systemic circulation over time. For two orally administered drug products to be bioequivalent, the active drug ingredient or active moiety in the test product must exhibit the same rate and extent of absorption as the reference drug product (2).

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 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 (3, 4).

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 (5).

Finofibrate is an oral antihyperlipemic 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) (6).

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 investigational formulation of Finofibrate 145 mg Tablets (manufactured by manufactured by Wockhardt Limited, India) and reference formulation 'Finofibrate ® '145 mg Tablet (® indicates reference formulation). 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 investigational formulation of Finofibrate 145 mg Tablets (manufactured by manufactured by Wockhardt Limited, India) and reference formulation 'Finofibrate ® '145 mg Tablet (® indicates reference formulation).

## MATERIALS AND METHODS

### 2.1 Study design

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

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'& 'B' and reference drug 'C' was studied in investigation. Subjects were checked in to the facility three times separated by washout period. All the subjects will be randomly assigned any of the 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 (7).

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.

### 2.2 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. Exclusion criteria of subject were as follows-

- Personal / family history of allergy or hypersensitivity to test drug or its congeners or history if any hypersensitivity or intolerance.
- Evidence of impairment of renal, hepatic, cardiac, lungs or gastrointestinal function
- Volunteers with clinically significant abnormal values of laboratory parameters.
- History of any psychiatric disorders.
- Consumption of alcohol within 48 hours prior to dosing or difficulty in abstaining alcohol for the duration of the study. Any indication of the regular use of more than one unit of alcohol per day (one unit = 150 ml of wine or 360 ml of Beer or 45 ml of alcohol 40%).
- Smokers, who smoke more than 10 cigarettes / day or inability to abstain from smoking during the study.
- Participation in any clinical trial within past three months.
- Donation of blood (1 unit or 350 ml) within 90 days prior to receiving the first dose of study medication
- Receipt of any prescription drug therapy or over-the-counter (OTC) drugs two weeks prior to receiving the first dose of study medication or repeated use of drugs within the last two weeks.
- Difficulty in swallowing solids like capsules or tablets.
- Inaccessibility of veins in left or right arm.
- Use of any recreational drugs or history of drug addiction or which in the opinion of the Investigator, would compromise the safety of the subject or the study
- Consumption of products like coffee, tea, cola drinks, chocolate (containing Xanthine), tobacco and cigarettes (containing nicotine), food or beverages prepared from grapefruit or grapefruit juice within 48 hours prior to receiving study medication.
- Having significant disease by referring medical history or physical examination during screening.

### 2.3 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.

**Table No. 1 Individual Drug-Dose Information**

| 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 No.2 Schematic representation of the study schedule for safety assessment And blood collection in period I/II/III**

| 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).*

The subjects were dosed next morning with the investigational product (IP) in the study after they have maintained 10hr fasting as per protocol. Dosing was done according to the randomization schedule. The randomization code for the dosing was generated by the statistician in which the sequence of IP administration was mentioned ("ABC" or

"BCA" or "CAB".) in Table No.1. The subjects were dosed as per schedule (Table No.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.

**2.4 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 No.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 (8).

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 [NPP (National Pharmacovigilance Protocol), 2003, Ministry of Health and Family Welfare govt. of India].

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 (8).

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 (9).

**2.5 Assessments**

**2.5.1 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 h) 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 no.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 $^0$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.

**2.5.2 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 (10).

## 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 & Biopharmaceutics Department of Wockhardt Ltd, India.

The tables (Table No. 3 and 4) and figures (Fig. No. 1 and 2) illustrate pharmacokinetic and statistical and mean graph obtained for Drug Finofibrate.

**Table No. 3 Pharmacokinetic results calculated for Drug Finofibrate**

| 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 |
| **$AUC_{0-\infty}$(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 |
| **$T_{½}$ (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 No.4 Summarized statistical values for Drug Finofibrate in 18 subjects**

| Parameter | $C_{max}$ (ng/mL) | $AUC_{0-t}$ (ng.hr/mL) | $AUC_{0-\infty}$ (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 |

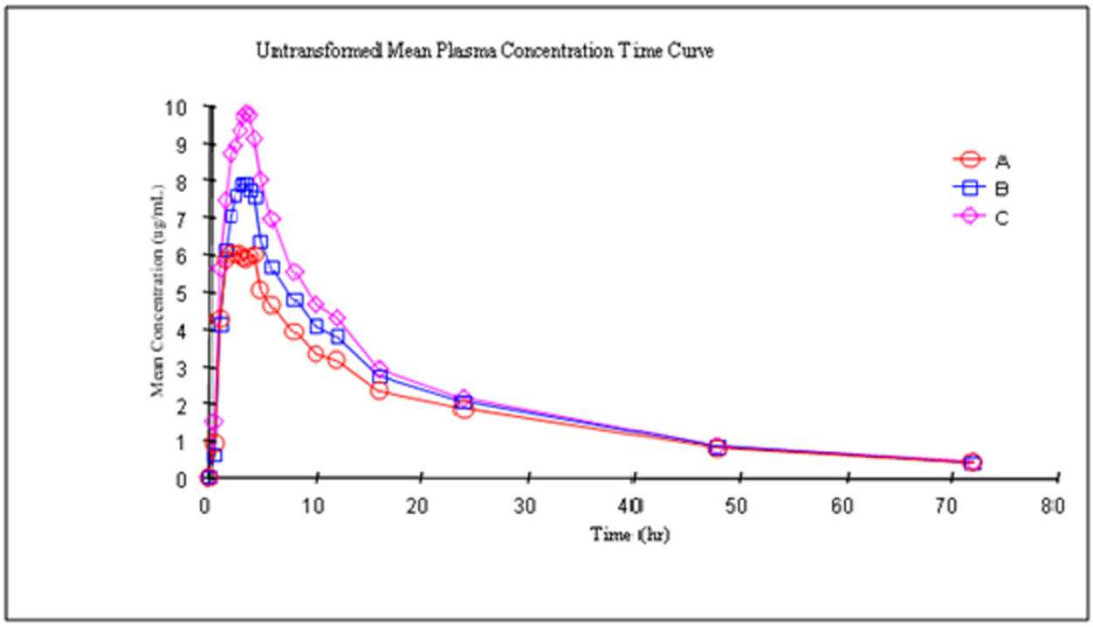


**Figure No.1 Linear Mean Plasma Concentration Time Curve of Drug Finofibrate**

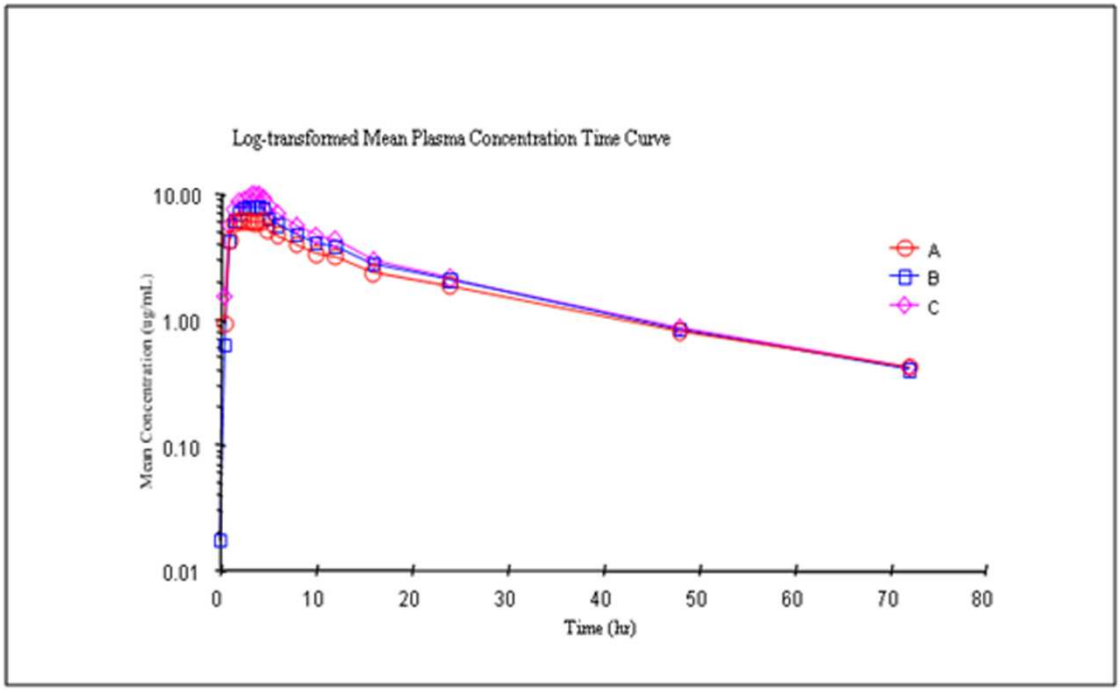


**Figure No. 2: Semi log-transformed Mean Plasma Concentration Time Curve for Drug Finofibrate**

**Pharmacokinetic Analysis**

**A. Area Under the plasma Concentration time curve ($AUC_{0-t}$, t=72hr) 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±55.899ng.h/ml The AUC0-t for reference product C ranged from 388.75 to 3244.16ng.h/ml with a Mean ±SD of 256.8569±83.2772ng.h/ml.

The geometric values for the test products A, test products B and reference product C were found to be 131.30ng.h/ml &145.48ng.h/ml & 165.75 ng.h/ml. respectively.

***Parent drug $AUC_{0-\infty}$:***

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

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

**B. 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$h^{-1}$ & 0.0969±0.017$h^{-1}$ for Test Product A & 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 & test products B & Reference Products C were found to be 0.04 $h^{-1}$ and 0.04 $h^{-1}$ & 0.04$h^{-1}$ respectively.

**C. 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 & 26.3192± 5.269 for Test Product A & 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 & test products B and Reference Products C were found to be 19.4 h &18.31 h and 17.58 h respectively.

**D. Residual Area (AUC_%Extrap_obs):**

***Parent Drug***

The Mean ± SD values of the Residual Area (%) were found to be 15.92±4.658 & 13.55± 3.535 for Test Product A & test products B and 15.85± 4.750 for Reference Product C.

**Statistical Results**

**A. 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 $AUC_{o\_\infty}$ were as follows:

***Parent drug (A)***

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

***Parent drug (B)***

LSM ratio $C_{max}$ 75.56 % & CI 68.88 % to82.89%, $AUC_{0-t}$ LSM ratio 88.82 % &82.29 % to 95.87 % and $AUC_{0-\infty}$ LSM ratio 89.19 % & 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.

**B. p-values (ANOVA)**

The p-value should be greater than 0.05 for Cmax, AUC0-t & $AUC_{0-\infty}$ 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& 0.8486), $AUC_{0-t}$ (0.6329&0.0136) and $AUC_{0-\infty}$ (0.5321&0.0143) which indicates no statistically significant differences were observed for sequence effect on pharmacokinetic parameters $C_{max}$ , $AUC_{0-t}$ and $AUC_{o-\infty}$.

**C. 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%.

**D. 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

**E. 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. The use of the -20% to 25% rule is based on a medical decision that for most of

the drugs, a -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, 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 inclusion and exclusion criteria. Non-compliance with study protocol. 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. 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 Finofibrate® 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 Drug Finofibrate and Drug 'Finofibrate ®' (® indicates reference formulation), thus lead to suggest that these two formulations are said to be bioinequivalent.

## 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 $C_{max}$, $AUC_{o-t}$ and $AUC_{0-\infty}$ when compared with reference formulation 145 mg 'Finofibrate ® 'Tablet.

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## REFERENCES

[1] CDSCO (Central Drug Standard Control Organization), Guidelines for Bioavailability and Bioequivalence, 2005. Retrieved from http://cdsco.nic.in/html/BE%20Guidelines%20Draft%20Ver10%20March%2016,%2005.pdf, accessed on 12 March **2008**.
[2] CDER (Center for Drug Evaluation & Research). Guidance for Industry: Bioavailability and Bioequivalence studies for orally administered Drug Products, **2003**.
Retrieved from http://www.fda.gov/CDER/guidance/5356fnl.pdf, accessed on 25 Feb **2008**.
[3] S. Andre, F. Scott, S. Devinder, C. Richard . *Advanced drug Delivery reviews*, **2003**; 56: 398-399.
[4] NAAS (National Academy on an Aging Society), **2000**. Retrieved From http:// www.agingsociety.org/agingsociety/pdf/depression.pdf, accessed on 23 Feb 2008.
[5] D. Frederickson, R. Lee.. *Journal of Hypertension*, 1965: 31:321-7.
[6] K. Tripathi. Hypolipidemic Drug And Plasma Expanders, Essential of Medical Pharmacology, 2004; 5:557.
[7] W. Cochran, G. Cox. *Experimental designs* **1957**; 11: 240-248.

[8] NPP (National Pharmacovigilance Protocol), Ministry of Health and Family Walfare govt. of India, **2000**. Retrieved from http://209.85.175.104/search?q=cache:3nyipCINCGoJ:cdsco.nic.in/html/Pharmacovigilance%2520Protocol%2520.pdf+National+Pharmacovigilance+Protocol+for+assessment+of+adverse+events&hl=hi&ct=clnk&cd=2&gl=in, accessed on 10 March **2008**.
[9] In house standard operating procedure (SOP) developed in CPB Wockhardt ltd. Mumbai, India.
[10] Bioavailability protocol guidelines for ANDA and NDA Submission. Division of Biopharmaceutics, USFDA (United States Food and Drug Administration), **1997**.