Chapter 1: Introduction
Chapter-I

Introduction

1.0 Introduction

The concept of generics has its origin in the need for access to affordable medicines for the population. The USFDA’s ‘Center for Drug Evaluation and Research’ [CDER] defines a generic drug as a drug product that is comparable to a brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics and intended use.

Generic drugs are frequently as effective as, but much cheaper than, brand-name drugs [WHO ‘Generic Drugs’]. Historically, generic drug products have been driven by the regulations and laws introduced by Governments of various countries the world over, primarily to make the medicines affordable and accessible. The generic drugs industry provides cheap affordable copies of brand-name medicines and has pushed down drug prices overall through competition. The ‘World Health Report 2012’ estimates that countries could save about 60% of their pharmaceutical expenditures by shifting from originator medicines to generic products [WHO - ‘World Health Report 2012’].

The concepts of bioavailability and bioequivalence, as regards the generic medicines, are scientific criteria to ensure appropriate standards like quality, efficacy and safety of generics.

Bioavailability is defined as 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 [U.S.FDA, 2003].
Chapter 1

The term ‘Bioequivalent Drug Product’ describes ‘pharmaceutical equivalent’ or ‘pharmaceutical alternative’ products that display comparable bioavailability when studied under similar experimental conditions. One set of conditions under which a test and reference listed drug shall be considered bioequivalent is that: the rate and extent of absorption of the test drug do not show a significant difference from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or the extent of absorption of the test drug does not show a significant difference from the extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the reference drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug [USFDA. Orange Book. 2013].

The scientific concepts of bioavailability and bioequivalence have evolved over a period of about last 40 years and have been accompanied by evolving regulatory requirements for approval of generic drug products. The concept of bioequivalence has been adopted by the pharmaceutical industry and several regulatory authorities throughout the world. Because of this, thousands of generic drugs have been manufactured and marketed by the industry after regulatory approval. A lot of advances have been made during these years in developing various approaches to assess bioequivalence through research that would assure high quality interchangeable and affordable drugs [Midha K.K. et al., 2009].

Depending on the formulation, molecule and other factors bioequivalence may be established by Pharmacokinetic, Pharmacodynamic and clinical studies. Pharmacokinetic approach is usually the most preferred method to establish bioequivalence.
Chapter 1

Introduction

CDER’s March 2003 guidance [USFDA. 2003. Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations] states that “Several in vivo and in vitro methods can be used to measure product quality BA [Bioavailability] and to establish BE [Bioequivalence]. In descending order of preference, these include pharmacokinetic, pharmacodynamic, clinical, and in-vitro studies. Product quality bioavailability and bioequivalence frequently rely on pharmacokinetic measures such as AUC and C_max that are reflective of systemic exposure”.

In practice, equivalence is indicated when key Pharmacokinetic parameters, used to establish rate and extent absorption of the test and reference products, fall within a preset confidence interval [Midha KK et al., 2009]. Currently the most widely accepted approach for establishing Bioequivalence, for most in-vivo Bioequivalence trials is the ‘Average Bioequivalence approach’. The average BE is recommended by guidances of most regulatory agencies like FDA, EMA, NPCB, etc for a comparison of BA measures in most BE studies.

The ‘Average Bioequivalence Approach’ was recommended, in the July 1992 guidance on Statistical Procedures for Bioequivalence Studies, using a standard two-treatment crossover design [U.S.FDA, 2001]. CDER’s March 2003 guidance [Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations] recommends single-dose, crossover studies as a design for BE studies. To compare measures in these studies, data have been analyzed using an average BE criterion. This guidance recommends continued use of an average BE criterion to compare BA measures for replicate and non-replicate BE studies of both immediate- and modified-release products.

Bioequivalence studies involve various phases including Clinical phase, Bioanalytical phase, Pharmacokinetic phase and Statistical analysis. In typical clinical phase, test and reference products are administered to healthy adult volunteers capable
of giving consent. The design and number of subjects enrolled are decided on a statistical basis. The common/usual study design is a 2-way crossover design; although different approaches and designs may be followed depending on the molecule and formulation. The two periods of the crossover are separated by an adequate washout period which is decided as per the half-life of the product.

The bioanalytical phase involves method development and method validation. For the analytical methods to be reliable and yield accurate dependable results, the analytical methods need to be well characterized, standardized, validated and documented. The method should be accurate, precise, selective, sensitive and reproducible. A validated method is used for actual analysis of samples to determine the concentration of drugs and/or metabolites in the matrix.

As recommended by regulatory guidelines, the key Pharmacokinetic parameters like the peak plasma concentration (C\text{\textsubscript{max}}), Area under plasma concentration-time curve (AUC) i.e. AUC\textsubscript{0-t} are measured and AUC extrapolated to infinity (AUC \textsubscript{0-\infty}) is calculated. The averages of one or more of these Pharmacokinetic parameters, is subjected to 90% confidence interval approach. The acceptance criteria of bioequivalence for non-narrow therapeutic range orally administered drugs Immediate-Release Products is that the 90% confidence interval for the ratio of the test and reference product averages of pharmacokinetic parameters C\text{max}, AUC\textsubscript{0-t} and AUC\textsubscript{0-\infty} should be between 80% and 125% for the log transformed data [U.S.FDA, 2003].

Similarly, the ‘Malaysian guidelines for the conduct of bioavailability and bioequivalence studies’ recommend an acceptance range of 0.80 - 1.25 for 90% confidence interval for AUC-ratio for orally administered, non-narrow therapeutic range products and permit a wider acceptance range for C\text{max}-ratio, with a justification in the protocol taking into account safety and efficacy considerations [Ministry of Health, Malaysia. 2000].
Levofloxacin is the L-isomer of the racemate, ofloxacin. The antibacterial activity of ofloxacin resides primarily in the L-isomer. It is indicated in adults (≥18 years of age) with infections caused by designated susceptible bacteria viz. Pneumonia (nosocomial and community acquired), Acute bacterial sinusitis, Acute bacterial exacerbation of chronic bronchitis, Skin and skin structure infections (complicated and uncomplicated), Chronic bacterial prostatitis, Urinary tract infections (complicated and uncomplicated), Acute pyelonephritis, Inhalational anthrax (post-exposure), Plague. The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination [USPI, 2012].

The fluoroquinolone class of antibacterial agents is among the most frequently prescribed drugs, with utility in a broad range of bacterial infections. Amongst fluoroquinolones, levofloxacin has low rates of some clinically important adverse events [Liu HH, 2010]. In 29 pooled Phase 3 clinical trials, 7537 patients were treated with levofloxacin, for a wide variety of infectious diseases at doses of 750 mg once daily, 250 mg once daily, or 500 mg once or twice daily, for usually 3 to 14 days (mean 10 days). The overall incidence, type and distribution of adverse reactions were similar in patients receiving the different doses. The most common adverse drug reactions (≥3%) were nausea, headache, diarrhea, insomnia, constipation, and dizziness [USPI, 2012].

The present study was planned to compare the bioequivalence of single dose of generic levofloxacin 500 mg tablets (Loxof tablets 500 mg), manufactured by Ranbaxy (M) SDN. BHD., with reference innovator product Cravit® tablets 500 mg (containing levofloxacin 500 mg), manufactured by PT. Kalbe Farma Tbk., in healthy, adult human subjects under fasting condition.