

## **Generic Drugs and Bioequivalence for its approval**

K.H.Barve\*<sup>1</sup> and Nidhiben Trangdiya<sup>1</sup>

1- School of Pharmacy and Technology Management,SVKM's NMIMS, V.L.Mehta road, Vile Parle (W), Mumbai- 400 056

\*e-mail: barve.kalyani@gmail.com

### **Summary**

A generic drug is a drug which is produced and distributed without patent protection.<sup>(3)</sup> According to the U.S. Food and Drug Administration (FDA), generic drugs are identical or within an acceptable bioequivalent range to the brand name counterpart with respect to pharmacokinetic and pharmacodynamic properties<sup>(3)</sup>. Generic pharmaceutical products need to confirm to the same standards of quality, efficacy and safety as required of the originator's (innovator) product.

Bioequivalence studies are the preliminary requirement for generic products to enter in the market. Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical and clinical data to establish safety and effectiveness.<sup>(7)</sup> Plasma time concentration curve is used to assess the rate and extent of absorption of the study drug. This includes primary pharmacokinetics parameters such as  $C_{max}$ ,  $T_{max}$ ,  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ . To be considered bioequivalent, test product/reference product ratio & the 90% confidence interval of these primary parameters should fall within the interval 80.00% to 125.00%<sup>(15)</sup>. The present manuscript provides information about generic drugs and important aspects involved in bioequivalence and regulatory requirement for bioequivalence study.

**Key words:** Generic drugs, Bioavailability & Bioequivalence.

### **Introduction**

A generic drug is a pharmaceutical product, usually intended to be interchangeable with an innovator product that is manufactured without a license from the innovator company and marketed after the expiry date of the patent or other exclusive rights. Generic drugs are marketed under a non-proprietary or approved name rather than a proprietary or brand name. Generic drugs are frequently as effective as, but much cheaper than, brand-name drugs.

Global generics market was valued at USD63.66 billion during 2005, registering a growth of 20% over the year 2004, which is 4 times that of patented drugs, which grew at 5% in the same period. North America was the major generics market accounting for about half of the global market in 2005. The US market alone accounted for 44% of the total generics market growing at a rate of 26% in 2005 over the previous year. The global market for generic drugs was worth \$84 billion in 2009, a figure that is expected to reach \$129.3 billion in 2014, for a compound annual growth rate (CAGR) of 9% over the 5-year forecast period.<sup>(1,2)</sup>

From time to time, controversies and claims arise regarding generic prescribing and generic substitution (3).

- Generic substitution may impair safety and efficacy of treatment
- Generic substitution may be dangerous for patients with life-threatening diseases
- Patients for whom a medication has been substituted should be carefully monitored.

These concerns make it worthwhile to revisit the issues and to try and sort fact from opinion and fiction.

### **What are generics?**

The term 'generic product' is used in different ways. A common use of the term (and that used by the World Health Organization (WHO)), is for a pharmaceutical product that is (3,4)

- Intended to be interchangeable with the innovator product in an individual patient
- Usually manufactured without a license from the innovator company
- Marketed after expiry of patent or other exclusivity rights.

The WHO refers to these products as 'multisource pharmaceutical products'. To be interchangeable such products must be bioequivalent.

### **When can a generic drug be produced?**

When a pharmaceutical company first markets a drug, it is usually under a patent that allows only the pharmaceutical company that developed the drug to sell it. Generic drugs can be legally produced for drugs where: 1) the patent has expired, 2) the generic company certifies the brand company's patents are either invalid, unenforceable or will not be infringed, 3) for drugs which have never held patents, or 4) in countries where a patent(s) is/are not in force. The expiration of a patent removes the monopoly of the patent holder on drug sales licensing. Patent lifetime differs from country to country, and typically there is no way to renew a patent after it expires. A new version of the drug with significant changes to the compound could be patented, but this requires new clinical trials. In addition, a patent on a changed compound does not prevent sales of the generic versions of the original drug unless regulators take the original drug off the market.

This allows the company to recoup the cost of developing that particular drug. After the patent on a drug expires, any pharmaceutical company can manufacture and sell that drug. Since the drug has already been tested and approved, the cost of simply manufacturing the drug will be a fraction of the original cost of testing and developing that particular drug.

### **Challenging patents**

Brand-name drug companies have used a number of strategies to extend the period of market exclusivity on their drugs, and prevent generic competition. This may involve aggressive litigation to preserve or extend patent protection on their medicines, a process referred to by critics as "evergreening". Patents are typically issued on novel pharmacological compounds quite early in the drug development process, at which time the 'clock' to patent expiration begins ticking. Later in the process, drug companies may seek new patents on the production of specific forms of these

compounds, such as single enantiomers of drugs which can exist in both “left-handed” and “right-handed” forms, different inactive components in a drug salt (5) or a specific hydrate form of the drug salt. (6) If granted, these patents ‘reset the clock’ on patent expiration. These sorts of patents may later be targeted for invalidation (“paragraph IV certification”) by generic drug manufacturers. (3)

**Generic drug exclusivity**

The U.S. Food and Drug Administration offers a 180 day exclusivity period to generic drug manufacturers in specific cases. During this period only one (or sometimes a few) generic manufacturers can produce the generic version of a drug. This exclusivity period is only used when a generic manufacturer argues that a patent is invalid or is not violated in the generic production of a drug, and the period acts as a reward for the generic manufacturer who is willing to risk liability in court and the cost of patent court litigation. There is often contention around these 180 day exclusivity periods because a generic producer does not have to produce the drug during this period and can file an application first to prevent other generic producers from selling the drug. (7)

**Interchangeability and Substitution**

Theoretically, any generic drug that is bioequivalent to its trade-name counterpart may be interchanged with it. For drugs that are off-patent, the generic drug may be the only form available. To limit costs, many doctors write prescriptions for generic drugs whenever possible. Even if the doctor has prescribed a trade-name drug, the pharmacist may dispense a generic drug unless the doctor wrote on the prescription that no substitution can be made. Also, insurance plans and managed care organizations may require that generic drugs be prescribed and dispensed whenever possible to save money. Some plans may allow a consumer to select a more expensive trade-name product prescribed by the doctor as long as the consumer pays the difference in cost. (8,9)

Sometimes generic substitution may not be appropriate. For example, some available generic versions may not be bioequivalent to the trade-name drug. Such generic drugs may still be used, but they may not be substituted for the trade-name product. In cases in which small differences in the amount of drug in the bloodstream can make a very large difference in the drug's effectiveness, generic drugs are often not substituted for trade-name drugs, although bioequivalent generic products are available. Warfarin (COUMADIN), an anticoagulant, and phenytoin (DILANTIN), an anticonvulsant, are examples of such drugs. Finally, a generic product may not be appropriate if it contains an inactive ingredient that the person is allergic to. (10,11)

Drugs that must be given in very precise amounts are less likely to be interchangeable, because the difference between an effective dose and a harmful or an ineffective dose (the margin of safety) is small. Digoxin (LANOXIN), used to treat people with heart failure, is an example. Switching from the trade-name version of digoxin(LANOXIN) to a generic product may cause problems, because the two versions may not be sufficiently bioequivalent. However, some generic versions of digoxin (LANOXIN) have been certified as bioequivalent by the FDA.

**Bioequivalence**

Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailability (rate and extent of availability) after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, can be expected

to be essentially the same. Pharmaceutical equivalence implies the same amount of the same active substance(s), in the same dosage form, for the same route of administration and meeting the same or comparable standards.

Product quality and bioequivalence data are required before a generic product can be registered. The quality data required include purity, stability, good manufacturing practice and quality control. These data are the same as those required for innovator products. It has sometimes been suggested that generic products may contain ratios of enantiomers (optical isomers) that are different from the innovator product. This argument cannot be sustained, as conventional chemical synthesis of the active drug produces a racemic (equal) mixture of the two enantiomers. Data on the enantiomeric ratio of the active substance in a generic product would in any case be required before registration.

Manufacturers seeking regulatory approval of competitive (generic) products (e.g. Abbreviated New Drug Application [ANDA]), must provide detailed bioavailability evidence showing head-to-head comparative performance of their product against the innovator's product. Such trials are fundamentally designed to establish clinical equivalence particularly as it relates to interchangeability or substitutability.

#### **COMPARATIVE BIOAVAILABILITY FOR GENERIC DRUG PRODUCTS (ANDA): BIOEQUIVALENCE STUDIES**

The design of and requirements in, bioequivalence studies are fundamentally satisfied through single dose administrations, although there is a lingering interest in multiple dose testing. The focus is on the rate and extent of absorption of the active ingredient, although some jurisdictions (e.g. FDA) continue to show an interest in the primary active metabolite(s). In some cases, notably drugs that exhibit non-linear pharmacokinetics, the dose strength to be tested may be dictated by whether the drug's non-linearity is attributable to the absorption or elimination phase (Health Canada). As a general principle, the studies are designed to test inherent product absorption properties. Thereby, the trials generally specify healthy normal controls that exhibit circumscribed demographics.

Comparative evidence may require not only studies in a fasting condition, but following a specified meal. The latter permit drug formulations to be evaluated under "stressed conditions". If it is shown that competitive products are bioequivalent under both fasting and fed conditions, there is greater confidence that they are therapeutically equivalent when used in patients.

#### **Requirements for testing competitive (generic) products (10,12,13)**

The following describes the requirements for most orally administered products, including tablets, capsules and modified-release dosage forms. Nevertheless, it is best to check with each regulatory agency regarding current or special drug- or product-specific requirements.

##### **A. Objectives**

To test the comparative bioavailability of a test and reference product and thereby to determine their equivalence.

### **B. Parameter to be determined**

For single dose study pharmacokinetic parameter  $C_{max}$ ,  $AUC_{0-t}$ ,  $AUC_{0-\infty}$  residual area  $T_{max}$ ,  $K_{el}$ ,  $t_{1/2}$  is determined using plasma time concentration profile of drug For multiple dose studies  $AUC_{(0-\infty)}$ ,  $C_{max,ss}$  and  $t_{max,ss}$  determined using plasma time concentration profile of drug(13,14).

### **C. Secondary endpoints**

Determine the time-dependent concentrations of potential important metabolites (active and contributing to the product's therapeutic response) in the collected blood (or plasma/serum) of each subject following administration of the test and reference products.

### **D. Exploratory endpoints**

Determine the  $C_{max}$ ,  $AUC_t$ ,  $AUC_{\infty}$ ,  $T_{max}$ ,  $\lambda_z$  and half-life of the primary (and secondary) endpoints following each of the test and reference products, for each subject.

### **E. Study design**

The study shall be designed in such a way that the effects of formulation can be distinguished from other factors. If two formulations are compared, a randomized two-period, two-sequence crossover study is considered the design of choice. An adequate washout period between periods is needed to avoid drug carryover effects. Alternative study designs include the parallel design for very long half-life substances or the replicate design for substances with highly variable disposition.

However, when it is recommended that the study drug be given with food (as would be in routine clinical practice), or where the dosage form is a modified release product, fed state studies need to be carried out in addition to the fasting state studies. Fed state studies are also required when fasting state studies make assessment of  $C_{max}$  and  $T_{max}$  difficult.

The fed study is to be designed in such a way that the effects of formulation can be distinguished from other factors. Normally, subjects fast for 10 hours prior to ingesting a standardized meal. The meal is to provide the greatest changes from the gastrointestinal physiology of a fasting state. A meal with high-fat and high-calorie content is recommended (e.g. 150, 250 and 500-600 calories from protein, carbohydrate, and fat, respectively). The meal shall be ingested over a period of 30 minutes or less. The product dose shall be ingested 30 minutes after start of the meal.

Normally, subjects fast for 10 hours prior to product administration. Normally, the highest safe strength/dose of the test or reference product will be administered at the start of an experimental day with about 8 ounces (240 mL) of water. Further fluid will be withheld for about 2 hours; standardized meals are to be permitted beginning at four hours after drug administration. All subsequent meals will be carefully standardized according to a fixed schedule.

For most drugs, subjects shall not be permitted to recline until at least two hours after product ingestion. Physical activity and posture is to be standardized to limit variable effects on gastrointestinal blood flow and motility. Blood samples (about 12 to 18, including a pre-dose sample) shall be drawn at appropriate, specified, and carefully recorded times (to capture increasing and decreasing concentrations during the absorption, distribution and elimination phases).

There should be at least three sampling points during the absorption phase, three to four at the projected  $T_{max}$  and four points during the elimination phase. The number of points used to calculate the terminal elimination rate constant should be preferably determined by a semi logarithmic plot. The collections are to continue for about three terminal drug half-lives in order to capture at least 80% of the total area. At least three to four samples need to be obtained from the terminal log-linear phase to derive an acceptable estimate of the terminal constant ( $\lambda_z$ ) from linear regression. For long half-life drugs, a truncated AUC (e.g. up to 72 hours) is generally considered adequate.

Where urinary excretion is measured in a single dose study it is necessary to collect urine for seven or more half lives.

#### **F. Planned sample**

While most jurisdictions support a minimum of 12 subjects in a bioequivalence trial, the likelihood of a successful outcome is improved with an increase in the subject number. The appropriate subject number can be forecast via the ANOVA error variance associated with the specific metric (e.g. from published data or a pilot study), the expected deviation of the test product's metric from that of the reference product (e.g. 0.05) and the bioequivalence criterion (e.g. 90% confidence that the estimated population mean ratio lies between 80 and 125%).

#### **G. Study population**

To minimize variability and focus on the comparison of the two formulations, healthy volunteers are to be selected, although for some drugs it may, of necessity, be best to conduct the trial in patients. Subjects will ordinarily be between 18 and 55 years of age and within the accepted normal range for Body Mass Index. Clinical laboratory tests, notably to assess cardiac, renal and hepatic function, are to be normal based on subject screening. Furthermore, subjects will have undergone an extensive review of medical history and received a comprehensive medical examination.

For drugs primarily intended for use in only males or only females volunteers of only respective gender should be included in the studies.

#### **H. Specific inclusion criteria**

Healthy males or females will be included in the study population. Preferably, non-smokers will be employed. (12,13)

#### **I. Specific exclusion criteria**

Women of childbearing potential are to be excluded if there is a potential risk. Subjects shall not have a history of alcohol or drug abuse. Subjects shall not be receiving drugs for any medical condition. There is to be no known allergy to the administered drug or formulation. As a rule, alcoholic beverages and over-the-counter drugs shall be avoided during the days immediately preceding a trial and for an appropriate interval during the active sample collection period of the trial. (15, 16)

#### **J. Tools for assessing primary endpoints**

A validated analytical method is needed for both the primary and secondary endpoints.

#### **k. Data analysis method**

All study information, including exploratory endpoints shall be presented for each subject following the test and reference products. ANOVA is to be used to identify the source contributions by

factors including subjects, period, formulation and potential interactions.<sup>(23)</sup> The geometric mean ratio together with the ANOVA residual mean error term are used to identify the statistical basis for the 90% confidence interval for the ratio of the population means (Test/Reference) of the identified metrics (e.g. AUC,  $C_{\max}$ ).

It is recommended that the 90% confidence intervals for the ratio of the test and reference products should be contained within the acceptance interval of 80–125% for  $C_{\max}$  and AUC. For drugs with a narrow therapeutic range, the acceptance interval may have to be narrowed to 90–111%.<sup>(17)</sup>

For highly variable drugs, regulatory authorities recognize that the 90% confidence intervals contained within 80% and 125% might be difficult to attain unless very high sample sizes of subjects are included. Therefore, a widened acceptance interval for  $C_{\max}$  might be considered in certain cases. The European Medicines Agency draft revised guideline stipulates that the acceptance for  $C_{\max}$  can be widened to 75–133% if  $C_{\max}$  is of less importance for the clinical efficacy and safety compared to AUC.<sup>(2)</sup>

### **Conclusion**

Today, various pharmaceutical companies developing generic drug products. Bioequivalence study is important for generic drug approval process. This review will provide an easy quick overview for Regulatory consideration required for bioequivalence study.

### **References**

- 1) Blume. H., Midha, K.K; Report of Consensus Meeting: Bio-international '92. Conference on Bioavailability, Bioequivalence and Pharmacokinetic Studies. Bad Homburg, Germany, Eur. J. Pharm. Sci., 1992;1, 165-171.
- 2) Boddy. A.W., Snikeris. F.C., Kringle. R.O., Wei. G.C.G., Oppermann. J.A., Midha. K.K., An approach for widening the bioequivalence acceptance limits in the case of highly variable drugs, Pharm. Res., 1995;12,1865-1868.
- 3) Donald J. Birkett, Generics – equal or not?, Adelaide Australian Prescriber, 2003; 26 (4).
- 4) "Generic Initiative for Value and Efficiency (GIVE)". FDA. October 4, 2007. "Generic medicines training kit: safe and appropriate use of generic medicines". Pharmaceutical Society of Australia Competency Standards for Pharmacists in Australia 2003. National Prescribing Service Limited (NPS). 2003-07-09. Approved Drug Products with Therapeutic Equivalence Evaluations, Preface. - an explanation of FDA terms and procedures
- 5) U.S. Patent 4,721,723: Paroxetine hydrochloride hemihydrate
- 6) U.S. Patent 4,879,303: Amlodipine besylate.
- 7) "Guidance for Industry: 180-Day Generic Drug Exclusivity Under the "Paragraph IV Drug Product Applications: Generic Drug Patent Challenge Notifications". FDA, Office of Generic Drugs (OGD). 2008-<http://www.fda.gov/cder/ogd/#paragraph>. Retrieved 2008-06-16.
- 8) Guidance for medication interchangeability of Mexican Official journal (1999) section I: 45-68.

- 9) Bioequivalence and Interchangeability of Generic Drugs Trade-Name and Generic Drugs Merck Manual Home Edition.mht
- 10) The Merck Manual for Healthcare Professionals Section – Clinical Pharmacology, Subject - Pharmacokinetics, Topic- Bioavailability.  
<http://www.merck.com/mmpe/sec20/ch303/ch303c.html>
- 11) Interchangeable multi-source pharmaceutical products. WHO draft guideline on marketing authorization requirements, December 1993.
- 12) Jigar Patel, Kritika Aneja, Ravi Tiwari, A review on bioavailability and bioequivalence trials and its necessity, International Journal of Pharmacy and Pharmaceutical Sciences, 2010 ;2,(3), 1-8.
- 13) Guidelines for Bioavailability and Bioequivalence, Government of India, Ministry of Health and Family Welfare, Directorate General of Health Services, CDECO (Central Drug Standard Control Organization), 2005
- 14) Code of Federal Regulations, Title 21-Food and Drugs, Volume 5, Revised as of April 1, 2009 CITE: 21CFR320.1 Chapter I--Food And Drug Administration, Department Of Health And Human Services. Subchapter D- Drugs For Human Use. Part 320 -- Bioavailability and Bioequivalence Requirements Subpart A—General Provisions.
- 15) FDA (U.S. Food and Drug Administration), CDER (Center for Drug Evaluation and Research). Guidance for Industry: Bioavailability bioequivalence for orally administered drug products and general considerations (Draft). 2002.
- 16) Asif M. Tamboli, Pavan Todkar, Priti Zope, Sayyad F.J., An Overview on Bioequivalence: Regulatory Consideration for Generic Drug Products, Journal of Bioequivalence & Bioavailability ,2010;2,86-92.
- 17) Jake J. Thiessen ,Leslie Dan Chapter 8. Bioavailability and Bioequivalence, [http://www.iuphar.org/pdf/hum\\_55.pdf](http://www.iuphar.org/pdf/hum_55.pdf)