CHAPTER-2

LITERATURE REVIEW
2.0. LITERATURE REVIEW

The available information related to the research topic and drug properties were collected and explained under the following headings.

2.1. Drug Profile - Gabapentin
2.2. Bioavailability and Bioequivalence study
2.4 Generic drugs
2.5 Drug Interchangeability

2.1. Drug Profile - Gabapentin

Gabapentin was approved as an add on treatment for partial seizures, with or without generalization seizure in 1993 by U.S.FDA. The other indication of Gabapentin is to treat the postherpetic neuralgia, which was approved by the U.S FDA in May 2002. Gabapentin has been used to treat a number of other conditions not approved by the FDA (off-label use), including neuropathic pain and exhibits high market sale. This outcome is not a new phenomenon since other AEDs have also been used to treat neuropathic pain. The other off-label uses of Gabapentin include bipolar mental disorder, various pain disorders, amyotrophic lateral sclerosis, attention-deficit disorder, migraine, drug and alcohol withdrawal seizures, restless leg syndrome, and first-line monotherapy for epilepsy. Gabapentin was approved for diabetic neuropathy in the EU region. In India, Gabapentin, the brand name Gabantin is indicated for the management of postherpetic neuralgia in adults. It is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy. It is also indicated as adjunctive therapy in the treatment of partial seizures in pediatrics of age 3 to 12 years.

The monograph of the Gabapentin from various drug information sources is discussed under the headings-description, mechanism of action, adverse effect and precaution, overdose, interaction, pharmacokinetics, use and administration. Some of the information is quoted in the text with their references.
Chapter 2

2.1.1 Description

Gabapentin is chemically 1-(aminomethyl) cyclohexaneacetic acid with a molecular formula of C9 H17N02 and a molecular weight of 171.3. Gabapentin is a white to off-white crystalline solid with a pKa1 of 3.7 and a pKa2 of 10.7. It is freely soluble in water and in alkaline and acidic solutions. A 2% solution in water has a pH of 6.5 to 8.0. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is -1.25. It is zwitterions that are structurally related to gamma amino butyric acid. Compound is stable at room temperature but a small amount of lactam formation occurs in aqueous solution. It has the following structure

![Gabapentin Structure](image)

2.1.2 Mechanism of action

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but it does not modify GABA\textsubscript{A} or GABA\textsubscript{B} radioligand binding, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation. The mechanism of action by which Gabapentin exerts its anticonvulsant and analgesic activities are not completely understood until 2002\textsuperscript{2} and more recently the alpha-2-delta-1 subunit of the voltage-dependent calcium channels has been identified as a binding target and produce pharmacological activity of antiepileptic, analgesic and anxiolytic properties in animal studies\textsuperscript{3}. However, functional correlates of Gabapentin binding, if any, remain to be elucidated.
2.1.3 Adverse Effects and Precautions

The most commonly reported adverse effects associated with gabapentin use are somnolence, dizziness, ataxia, and fatigue. Nystagmus, tremor, diplopia, amblyopia, pharyngitis, rhinitis, dysarthria, nausea and vomiting, weight gain, oedema, dyspepsia, amnesia, weakness, paraesthesia, arthralgia, purpura, leucopenia, anxiety, and urinary-tract infection may occur less frequently. Rarely, pancreatitis, altered liver function tests, erythema multiforme, Stevens-Johnson syndrome, myalgia, headache, and blood glucose fluctuations in diabetics have been reported. Common psychiatric effects include confusion, depression, and nervousness, and, more rarely, hallucinations and psychoses. Other adverse effects include acute renal failure, allergic reactions, alopecia, angioedema, chest pain, hepatitis, jaundice, movement disorders such as choreoathetosis, dyskinesia and dystonia, palpitations, thrombocytopenia, and tinnitus. Gabapentin should be used cautiously in patients with renal impairment and in those undergoing haemodialysis. False positive readings have been reported with some urinary protein tests in patients taking gabapentin. Care is required while withdrawing gabapentin therapy.

2.1.4 Incidence of adverse effects

A postmarketing surveillance study of 3100 patients taking gabapentin identified drowsiness or sedation as the most frequent adverse effect, occurring in about 6.7%. The incidences of other adverse effects were: headache, 3.6%; fatigue, 3.5%; nausea and vomiting, 2.6%; and dizziness, 2.4%. Less common adverse events included rash, visual defect, and ataxia. Overall, adverse effects were reported as the reason for stopping treatment in about 10% of patients. Of the 136 children aged under 12 years whose data were included in the study, the most frequently reported treatment-related adverse events were eczema, rash, and vomiting. In this study, none of the 11 infants born to mothers taking gabapentin throughout pregnancy had congenital abnormalities.
Gabapentin is fairly well tolerated in most patients. Adverse effects are primarily CNS-related, of mild to moderate severity at normal therapeutic doses and usually transient during continued therapy. The most frequent adverse events seen in 10-20% of patients were somnolence, dizziness, and ataxia. Similar adverse events are also seen with other antiepileptics, and are an extension of the pharmacological properties of the drug.

In placebo-controlled trials comparing gabapentin (900 mg to 3600 mg per day for 8 weeks) with placebo, gabapentin was found to be well tolerated. Adverse events experienced more frequently in the gabapentin group than in the placebo group were dizziness (24% vs 4.9%), somnolence (23% vs 6%) and confusion (8% vs 1.2%).

Gabapentin was well tolerated when given to healthy volunteers. In a randomized, placebo-controlled, double-blinded single dose trial done in 12 healthy volunteers comparing the analgesic effect of gabapentin (600 mg) with placebo, morphine (60 mg), and morphine + gabapentin, the observed adverse events with gabapentin were similar to placebo.

In another randomized, double blind, placebo controlled, single-dose cross-over trial in 25 healthy volunteers with gabapentin 1200 mg, lightheadedness was observed more frequently after administration of gabapentin than with placebo (7 vs. 2 subjects), and was rated as mild to moderate by all who experienced it. The incidence of other side effects (drowsiness, headache, decreased coordination, visual disturbances, and nausea) was not significantly different between gabapentin and placebo. Table 1 lists the treatment-emergent signs and symptoms that occurred in at least 1% of Gabapentin (Neurontin brand) treated patients with postherpetic neuralgia participating in placebo-controlled trials and these were numerically more frequent in the Neurontin group than in the placebo group. Adverse events were usually mild to moderate in intensity.
<table>
<thead>
<tr>
<th>#</th>
<th>Body system/preferred term</th>
<th>Neurontin N-336 (%)</th>
<th>Placebo N-227 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Body as a Whole</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>5.7</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>5.1</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>3.3</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>Accidental injury</td>
<td>3.3</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>2.7</td>
<td>2.6</td>
</tr>
<tr>
<td>2</td>
<td>Digestive System</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>5.7</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
<td>4.8</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>3.9</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>3.9</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>3.3</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Flatulence</td>
<td>2.1</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Metabolic and Nutritional Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peripheral edema</td>
<td>8.3</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>Weight gain</td>
<td>1.8</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia</td>
<td>1.2</td>
<td>0.4</td>
</tr>
<tr>
<td>3</td>
<td>Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>28.0</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>Somnolence</td>
<td>21.4</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>Ataxia</td>
<td>3.3</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Thinking abnormal</td>
<td>2.7</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Abnormal gait</td>
<td>1.5</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>In coordination</td>
<td>1.5</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Amnesia</td>
<td>1.2</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Hypoesthesia</td>
<td>1.2</td>
<td>0.9</td>
</tr>
<tr>
<td>4</td>
<td>Respiratory System</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pharyngitis</td>
<td>1.2</td>
<td>0.4</td>
</tr>
<tr>
<td>5</td>
<td>Skin and Appendages</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>1.2</td>
<td>0.9</td>
</tr>
<tr>
<td>6</td>
<td>Special Senses</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amblyopia</td>
<td>2.7</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Conjunctivitis</td>
<td>1.2</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Diplopia</td>
<td>1.2</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Otitis media</td>
<td>1.2</td>
<td>0.0</td>
</tr>
</tbody>
</table>

* *Reported as blurred vision*
2.1. 5 Carcinogenicity

It had been reported\(^\text{28}\) that studies on Gabapentin had been temporarily stopped in 1990 when pancreatic tumours were seen in rodent studies. However, the tumours were benign, occurred only with large doses, and were not thought to relate to humans.

2.1.6 Effects on the liver

There was report\(^\text{29}\) of a patient who developed cholestatic jaundice 2 weeks after starting therapy with Gabapentin 300 mg three times daily for diabetic neuropathy. Clinical symptoms and liver function tests improved on withdrawal of gabapentin.

2.1.7 Over-dosage

A 16-year-old girl complained of dizziness 6 hours after ingesting 48.9 g of gabapentin and was lethargic but arousable 2 hours later\(^\text{30}\). Her gabapentin plasma concentration was 62 micrograms/mL 8.5 hours after ingestion. By 18 hours she was alert and had no further complaints of lethargy or dizziness. In another report\(^\text{31}\) a patient with renal failure inadvertently received inappropriately high doses of gabapentin for 3 weeks and had a serum gabapentin concentration of 85 micrograms/mL without serious adverse effects. However, a patient with end stage renal disease who took twice extra doses of gabapentin between haemodialysis sessions developed marked somnolence and hypoxia severe enough to require intubation on both occasions: haemodialysis produced rapid improvement\(^\text{32}\).

A prospective observational study\(^\text{33}\) of gabapentin exposures reported to 3 poison centers has described a case series of 20 patients who took from 50 mg to 35 g of gabapentin alone. Of these, 12 experienced clinical symptoms including drowsiness, dizziness, gastrointestinal disturbance, hypotension, and mild tachycardia. These effects developed within 5 hours and lasted for less than 24 hours; toxicity was generally mild and there were no fatalities.
2.1.8 Drug Interactions

The absorption of gabapentin from the gastrointestinal tract is reduced by antacids containing aluminium with magnesium; it is recommended that gabapentin is to be taken at least 2 hours after taking any such antacid. Morphine has been reported to reduce the clearance of gabapentin; patients receiving both drugs should be monitored for signs of CNS depression and doses should be reduced accordingly. Cimetidine has also been reported to reduce the renal clearance of gabapentin, but licensed product information does not consider this to be of clinical importance.

2.1.9 Pharmacokinetics

Bioavailability of Gabapentin is not dose proportional; i.e., as the dose is increased the bioavailability decreases. Bioavailability of Gabapentin is approximately 60%, 47%, 34%, 33%, and 27% following 900, 1200, 2400, 3600, and 4800 mg/day given in 3 divided doses respectively. Gabapentin is absorbed from the gastrointestinal tract by means of a saturable mechanism. After multiple dosing the peak plasma concentrations (C\text{max}) are usually achieved within 2 to 3 hours of a dose and steady state achieved within 1 to 2 days. Gabapentin is not appreciably metabolized and most of the dose is excreted unchanged in the urine. Gabapentin is widely distributed throughout the body, but binding to plasma proteins is minimal. The elimination half-life (T_{1/2}) has been reported to be about 5 to 7 hours. Gabapentin is distributed into breast milk.

A study of the pharmacokinetics of single doses of gabapentin in healthy children aged 1 month to 12 years found that peak plasma concentrations occurred 2 to 3 hours after the dose in all age groups but that the mean value was higher in those older than 5 years than in younger children and the exposure was calculated to be about 30% less in the younger age group. As a result it was suggested that the initial dose of gabapentin in studies of safety and efficacy should be 40 mg/kg daily in children aged from 1 month up to 5 years, and 30 mg/kg
daily in children aged 5 to 12 years. (For licensed doses, see Administration in children, below.) A pharmacokinetic study in children with uncontrolled seizures (aged from 3 to about 15 years) also found a markedly higher mean oral clearance of gabapentin when compared to adults.

The pharmacokinetics of gabapentin was studied in 6 women and in their offspring during pregnancy, delivery, and breastfeeding. Findings suggested that gabapentin is actively transported across the placenta and accumulates in the fetus although its effect was unclear. All the deliveries, including one preterm, were uneventful and all of the infants were healthy, apart from one who became cyanosed and mildly hypotonic 8 hours after birth.

The distribution of gabapentin into breast milk was extensive and neonates were found to have a lower capacity to eliminate Gabapentin than adults, with an elimination half-life of about 14 hours. However, the plasma concentrations in the breast-fed infants appeared to be low and the relative infant dose was estimated to be 1.3 to 3.8% of the mothers' weight-adjusted dose at 0.2 to 1.3 mg/kg daily. No adverse effects were reported in the infants, and the authors considered that gabapentin was generally safe during breastfeeding.

Table 2 shows the pharmacokinetics of single dose oral bioavailability of Neurontin 300 mg immediate release capsule formulation in healthy human male participants.
There is no published data about the pharmacokinetics of Gabapentin in Indian population. The above data were from Thai and Korean populations.

2.1.10. Plasma drug concentration and effect relationship

Plasma Gabapentin concentrations in clinical trials have ranged from 2-20 mg/mL. While there is evidence of a dose for therapeutic effect relationship against partial seizures, plasma concentrations are not predictive of clinical efficacy or safety. Given the lack of interactions with other antiepileptic drugs there is no indication that therapeutic drug monitoring is likely to be useful.

2.1.11 Uses and Administration

Gabapentin is an antiepileptic used as a monotherapy or adjunctive therapy in the treatment of partial seizures with or without secondary generalization. It is not generally considered
effective for absence seizures. Although gabapentin is an analogue of gamma-aminobutyric acid (GABA), it is neither a GABA agonist nor an antagonist. Gabapentin is also used in the treatment of diabetic neuropathy.

In the UK, the initial oral dose of gabapentin for the treatment of epilepsy is 300 mg on the first day of treatment, 300 mg twice daily on the second day, and 300 mg three times daily on the third day; thereafter the dose may be increased in increments of 300 mg every 2 to 3 days until effective antiepileptic control is achieved, which is usually within the range of 0.9 to 3.6 g daily. Higher doses of up to a maximum of 4.8 g daily have been reported to be well tolerated. Similar doses are used in the USA. The total daily dose should be taken in three equally divided doses and the maximum dosage interval should not exceed 12 hours.

In the treatment of neuropathic pain, doses should be titrated to a usual maximum of 1.8 g daily in three divided doses, in a similar manner to that recommended above for the treatment of epilepsy. Higher doses have sometimes been given. As with other antiepileptics, withdrawal of Gabapentin therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. Licensed product information recommends reducing the dose gradually over at least 7 days. Dosage of gabapentin should be reduced in patients with renal impairment. Gabapentin enacarbil (XP-13512) has been investigated as a prodrug of gabapentin. In the UK, for the treatment of partial seizures with or without secondary generalization, Gabapentin is licensed for use as adjunctive therapy in children aged 6 years and over and as monotherapy in those aged 12 years and over. As adjunctive therapy, gabapentin may be given in an initial oral dose of 10 to 15 mg/kg daily, titrated over a period of about 3 days until effective antiepileptic control is achieved, which is usually within the range 25 to 35 mg/kg daily. Higher doses of up to a maximum of 50 mg/kg daily have been reported to be well tolerated. Although not licensed for use in younger children, the BNF suggests that similar initial doses may be used in those aged 2 to 12 years; maintenance doses of 10 to 20 mg/kg 3 times daily (up to 900 mg daily for children weighing 36 kg or under, or 1.2 g daily for those over 36 kg) are also recommended. Older children may be given the usual adult
dosage regimen titrated to a maximum of 2.4 g daily. When used as monotherapy, the usual adult dosage regimen is given.

In the USA, gabapentin is licensed for adjunctive use in children aged 3 years and over. Initial doses are as in the UK; the maintenance dose for children aged 3 to 4 years is 40 mg/kg daily, and for those aged 5 years and over is 25 to 35 mg/kg daily. Children aged 12 years and over may be given the usual adult dosage regimen. The total daily dose should be taken in 3 equally divided doses and the maximum dosage interval should not exceed 12 hours. For a pharmacokinetic study suggesting that initial doses in younger children should be proportionately higher than in older ones.

Reduced doses of gabapentin are recommended for patients with renal impairment or those undergoing haemodialysis. Licensed UK product information recommends the following maintenance doses based on creatinine clearance and should be given in 3 divided doses:

- Creatinine clearance 50 to 79 mL/minute: 600 to 1800 mg daily
- Creatinine clearance 30 to 49 mL/minute: 300 to 900 mg daily
- Creatinine clearance 15 to 29 mL/minute: 300 mg on alternate days to 600 mg daily
- Creatinine clearance less than 15 mL/minute: 300 mg on alternate days to 300 mg daily

For those undergoing haemodialysis and who have never received gabapentin, the recommended loading dose is 300 to 400 mg followed by 200 to 300 mg after each 4 hour of haemodialysis. On dialysis-free days no doses of gabapentin should be given.

Gabapentin has relieved some of the neurological symptoms associated with cigarette poisoning. Gabapentin is used in epilepsy as adjunctive therapy for partial seizures with or without secondary generalization in patient's refractory to standard antiepileptic.

Dosage is adjusted against clinical response rather than by monitoring blood concentrations. Gabapentin is also used as monotherapy in partial epilepsy. Its efficacy as adjunctive treatment of generalized seizures remains to be determined. Gabapentin has been found to be
effective as adjunctive therapy in children with refractory partial seizures. Benefit has been reported from the use of Gabapentin in the prophylaxis of migraine. Gabapentin may also be effective in the management of cluster headache and have been tried in the prophylaxis of chronic daily headache.

Gabapentin appears to be of benefit in the management of hot flushes associated with the treatment of breast cancer. A study involving 420 women with breast cancer experiencing hot flushes (excluding women on active chemotherapy, but most of whom were receiving adjuvant endocrine therapy), found that a dose of 900 mg daily in three divided doses for 8 weeks was effective, although a dose of 300 mg daily was not. There is also evidence of benefit from gabapentin in the same dose (900 mg daily) in women experiencing hot flushes as a symptom of menopause. Another randomized placebo-controlled study found gabapentin 2.4 g daily to be as effective as conjugated estrogens 625 micrograms daily in the treatment of hot flushes in postmenopausal women. The severe self-mutilation that occurs in patients with Lesch-Nyhan syndrome has been reported to improve in those given antiepileptics such as gabapentin.

Interest has been shown in Gabapentin as a potential therapy for amyotrophic lateral sclerosis because it may inhibit glutamate formation\(^{39}\). The results from an early study demonstrated a trend towards a beneficial effect; however, a randomized trial\(^{40}\) failed to confirm any benefit from gabapentin on disease progression or symptoms.

Gabapentin has been found to control pain, spasm, and spasticity in patients with multiple sclerosis. It may also be of benefit in acquired nystagmus secondary to multiple sclerosis. Antiepileptics are among the drugs used to manage neuropathic pain, which is often insensitive to opioid analgesics. Although carbamazepine appears to be the usual choice, gabapentin is also given in the treatment of neuropathic pain including central pain, complex regional pain syndrome, postherpetic neuralgia, trigeminal neuralgia, and painful diabetic neuropathy.
While some overall ratings of Parkinson's disease appeared to be improved by gabapentin in a double blind study involving 19 patients with advanced Parkinsonism, improvements in individual signs and symptoms were not significant\(^1\). It was also reported that 5 of 6 other patients with progressive supranuclear palsy had experienced worsening of their disease when given gabapentin. Another study\(^2\) in 15 patients with motor complications failed to find any clinically significant benefit from gabapentin therapy.

There is growing interest in the use of analgesic adjuvants including antiepileptics such as Gabapentin to modulate opioid dosage and efficacious for postoperative pain. A systematic review considered that the evidence of benefit for gabapentin in acute pain was lacking, and noted that more effective analgesics for this indication were available\(^3\). However, a later systematic review found that preoperative use of Gabapentin effectively reduced opioid consumption and postoperative pain; further studies were considered warranted. It has been suggested that preoperative use of gabapentin may have other benefits, including pre-operative anxiety, attenuation of the haemodynamic response to intubation, and reduction in postoperative nausea and vomiting\(^4\)–\(^6\).

Gabapentin has psychotropic properties and has been tried in the management of several psychiatric disorders, including as an adjunct in the treatment of resistant depression and in the treatment of post-traumatic stress disorder. Although early open studies found that gabapentin may be of benefit in patients with bipolar disorder\(^7\) randomized controlled trials have so far failed to confirm this effect\(^8\).

The etiology of restless legs syndrome is obscure and treatment has been largely empirical. Two small randomized double-blind crossover studies\(^9\),\(^10\) found 6 weeks of treatment with gabapentin to produce improvement in symptoms; in patients undergoing haemodialysis the effects were seen with a dose of 300 mg after each of the 3 dialysis sessions per week although in patients with idiopathic disease the mean effective dose was 1.855 g daily. A prodrug of gabapentin, gabapentin enacarbil, is reported to be under investigation for the treatment of restless legs syndrome.
Chapter 2  

Literature Review

Gabapentin may be of benefit in some patients with fibromyalgia. In a randomized controlled study treatment with oral gabapentin 1.2 to 2.4 g daily in 75 patients produced a greater improvement in mean pain score over 12 weeks than placebo in 75 controls\textsuperscript{51}. Sleep problems were also improved, but there was no difference between the groups on a depression rating scale. The drug was generally well tolerated.

Gabapentin may improve the symptoms of stiff-man syndrome in patients unable to tolerate benzodiazepine therapy. A beta blocker is often the first drug used in patients with essential tremor who require regular treatment; however, gabapentin has also been tried with some success\textsuperscript{52}.

2.2. BIOAVAILABILITY AND BIOEQUIVALENCE STUDY (BA/BE STUDY)

2.2.1. Bioavailability (BA)

Bioavailability is a pharmacokinetic term that describes the rate and extent to which the active drug ingredient is absorbed from a drug product and becomes available at the site of drug action. Since pharmacologic response is generally related to the concentration of drug at the receptor site, the availability of a drug from a dosage form is a critical element of a drug product's clinical efficacy. However, drug concentrations usually cannot be measured directly at the site of action. Therefore, most bioavailability studies involve the determination of drug concentration in the blood or urine. This is based on the principle that the drug at the site of action is in equilibrium with the drug in the blood. It is therefore possible to obtain an indirect measure of drug response by monitoring drug levels in the blood or urine. Thus, bioavailability is concerned with how quickly and how much of a drug appears in the blood after a specific dose is administered. The bioavailability of a drug product often determines the therapeutic efficacy of that product since it affects the onset, intensity and duration of therapeutic response of the drug.

In bioavailability studies, the shape and the area under the plasma concentration versus time curves are mostly used to assess rate (Cmax, tmax) and extent (AUC) of absorption.
2.2.2. Bioequivalence (BE)

Bioequivalence is a relative term. It is defined as the absence of 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 and under similar conditions in an appropriately designed study. In bioequivalence studies, the primary question is to compare measures of release of drug substance between the test and the reference product. Hence bioequivalence is primarily a product quality question.

2.2.3. Methods to document BA/BE study

Several in vivo and in vitro methods can be used to measure product quality BA and to establish BE. In descending order of preference, these include

1. In vivo studies
   a. Pharmacokinetic
   b. Pharmacodynamic
   c. Clinical study

2. In vitro study (Dissolution study)

The definitions of BA and BE, expressed in terms of rate and extent of absorption of the active ingredient or moiety to the site of action, emphasize the use of pharmacokinetic measures in an accessible biological matrix such as blood, plasma, and/or serum to indicate release of the drug substance from the drug product into the systemic circulation. This approach rests on an understanding that measuring the active moiety or ingredient at the site of action is generally not possible and, furthermore, that some relationship exists between the efficacy/safety and concentration of active moiety and/or its important metabolite or metabolites in the systemic circulation.
To measure BA and establish BE, reliance on pharmacokinetic measurements may be viewed as a bioassay that assesses release of the drug substance from the drug product into the systemic circulation. A typical study is conducted as a crossover study. In this type of study, clearance, volume of distribution, and absorption, as determined by physiological variables (e.g. gastric emptying, motility and pH) are assumed to have less interoccasion variability compared to the variability arising from formulation performance. Therefore, differences between two products because of formulation factors can be determined.

Pharmacodynamic studies are not recommended for orally administered drug products when the drug is absorbed into the systemic circulation and a pharmacokinetic approach can be used to assess systemic exposure and establish BE. However, in those instances where a pharmacokinetic approach is not possible, suitably validated pharmacodynamic methods can be used to demonstrate BE.

Where there are no other means, well-controlled clinical trials in humans can be useful to provide supportive evidence of BA or BE. However the use of comparative clinical trials as an approach to demonstrate BE generally be considered insensitive and be avoided where possible. The use of BE studies with clinical trial endpoints can be appropriate to demonstrate BE for orally administered drug products when measurement of the active ingredients or active moieties in an accessible biological fluid (pharmacokinetic approach) or pharmacodynamic approach is infeasible.

Under certain circumstances, BA and BE can be documented using *in vitro* approaches for highly soluble, highly permeable, rapidly dissolving, and orally administered drug products. Documentation of BE using an *in vitro* approach (dissolution studies) is appropriate based on the biopharmaceutics classification system.

### 2.2.4. Design and conduct of PK BE study

A two-period, two-sequence, single-dose, cross-over, randomized design is the first choice for Pharmacokinetic Bioequivalence (PK BE) studies. Each subject is given the test and the
reference product in randomized order. An adequate wash-out period should follow the administration of each product. The interval (wash-out period) between doses of each formulation should be long enough to permit the elimination of essentially the entire previous dose from the body. The wash-out period should be the same for all subjects and should normally be more than five times the terminal half-life of the API. Consideration will need to be given to extending this period if active metabolites with longer half-lives are produced and under some other circumstances.

After administration of either the test or reference product, a series of samples are taken from each subject to determine concentrations of the active ingredient from each formulation. Sampling is typically performed by collection of blood, although urine may be collected in certain cases. HC guidance specifies that urine be used when blood concentrations of the study drug are too dilute to be detected accurately and when more than 40% of the study drug is eliminated unchanged in the urine. In most cases the exclusive use of urine excretion data should be avoided as this does not allow estimation of the \( t_{\text{max}} \) and \( C_{\text{max}} \) concentration. Sampling time should correspond to 80% of the Area Under the Curve (AUC), a measure of the total amount of drug in circulation over time.

The duration of study periods is largely indicated by the number of samples that are required to characterize the absorption, distribution, and elimination phases of the study drug. Sampling should be identical for each period and should begin with a pre-dose sample, generally taken within an hour prior to study drug administration, to obtain baseline values.

The exact timing of sample collection during each period depends on the nature of the drug under investigation (e.g., the drug's half-life or absorption time), but should be timed such that specific pharmacokinetic variables can be accurately gauged, including the AUC, the maximum concentration of the drug in the blood \( (C_{\text{max}}) \), and the drug's half-life in the blood \( (T_{1/2}) \).

For most solid, oral formulations, bioequivalence should be demonstrated under fasting conditions. Fed bioequivalence studies are conducted when the reference product have food
effect and it needs to be administered with food for safety reasons. Formulation differences between the test and reference products can be more easily identified when subject variation has been minimized by standardization of a study’s procedure. The assessment of BE is dependent on appropriate evaluation of pharmacokinetic parameters and statistical conclusions.

2.2.4.1. Assessment of bioequivalent

In order for different formulations of the same drug substance to be considered bioequivalent, they must be equivalent with respect to the rate and extent of drug absorption. Thus, the two predominant issues involved in the assessment of bioequivalence are: the pharmacokinetic parameters that best characterize the rate and extent of absorption and, the most appropriate method of statistical analysis of the data.

2.2.4.1.1. Pharmacokinetic criteria

With regard to the choice of the appropriate pharmacokinetic characteristics, Westlake suggests comparison of the formulations should be made with respect to only those parameter(s) of the blood level profile that possess some meaningful relation to the therapeutic effect of the drug.

Exposure measures are defined relative to early, peak, and total portions of the plasma, serum or blood concentration-time profile as follows:

- Early Exposure
- Peak Exposure
- Total Exposure

**Early Exposure**: For orally administered immediate-release drug products, BE can generally be demonstrated by measurements of peak and total exposure. An early exposure measure may be informative on the basis of appropriate clinical efficacy/safety trials and/or
pharmacokinetic/pharmacodynamic studies that call for better control of drug absorption into the systemic circulation (e.g., to ensure rapid onset of an analgesic effect or to avoid an excessive hypotensive action of an antihypertensive). In this setting, partial AUC is used as an early exposure measure. The partial area is truncated at the population median of $T_{\text{max}}$ values for the reference formulation. At least two quantifiable samples are collected before the expected peak time to allow adequate estimation of the partial area.

**Peak Exposure:** The peak exposure is assessed by measuring the peak/maximum drug concentration ($C_{\text{max}}$) obtained directly from the data without interpolation.

**Total Exposure:** For single-dose studies, the measurement of total exposure is:

- Area under the plasma/serum/blood concentration-time curve from time zero to time $t$ ($AUC_{0-t}$), where $t$ is the last time point with measurable concentration for individual formulation.
- Area under the plasma/serum/blood concentration-time curve from time zero to time infinity ($AUC_{0-\infty}$), where $AUC_{0-\infty} = AUC_{0-t} + Ct/\lambda z$, $Ct$ is the last measurable drug concentration and $\lambda z$ is the terminal or elimination rate constant calculated according to an appropriate method. The terminal half-life ($t_{1/2}$) of the drug is also reported.

For steady-state studies, the measurement of total exposure is:

- The area under the plasma, serum, or blood concentration-time curve from time zero to time $\infty$ over a dosing interval at steady state ($AUC_{0-\infty}$), where $\infty$ is the length of the dosing interval.
- $C_{\text{max}}$: Maximum drug concentration
- $C_{\text{min}}$: Concentration at the end of a dosing interval
- Peak trough fluctuation: Percentage difference between $C_{\text{max}}$ and $C_{\text{min}}$.

$AUC$ and $C_{\text{max}}$ are considered to be the most relevant parameters for assessment of bioequivalence for single dose IR formulation. When urine samples are used, cumulative
urinary recovery (Ae) and maximum urinary excretion rate are employed instead of AUC and C_max.

2.2.4.1.2. Statistical criteria

After a bioequivalence study is conducted and the appropriate parameters are determined, the pharmacokinetic data must be examined according to a set of predetermined criteria to confirm or refute the bioequivalence of the test and reference formulations i.e., one must determine whether the test and reference products differ within a predefined level of statistical significance. Since the statistical outcome of a bioequivalence study is the primary basis of the decision for or against therapeutic equivalence of two products, it is critically important that the experimental data be analyzed by an appropriate statistical test.

Originally, bioequivalence was based on a demonstration that simple mean bioavailability parameters differed by less than 20% from the brand-name product. In 1977 this was modified to include a "power" approach that tested the null hypothesis that the rate and extent of bioavailability of the generic product was similar to the innovator product, and the power of the study was sufficient to detect at least a 20% difference.

In 1986, the FDA adopted the currently used average bioequivalence approach, which involves a Two One Side Test (TOST) procedure of 90% CI approach. For immediate-release oral dosage forms, the standard average bioequivalence determination employs a single-dose crossover study, typically conducted in a limited number of healthy volunteers. Results are analyzed according to whether the generic product (test), when substituted for the brand-name product (reference), is significantly less bioavailable, and alternatively, whether the brand-name product, when substituted for a generic product, is significantly less bioavailable (the two 1-sided tests). The core of the bioequivalence concept is an "absence of a significant difference." A difference > ± 20% is viewed by the FDA as significant. By convention, all data are expressed as a ratio of the average response (AUC and C_max) for test/reference, so the limit expressed in the second analysis is 125% (reciprocal of 80%). Tests are carried out using an analysis of variance and calculating a 90% confidence interval.
(Cl) for the average of each pharmacokinetic parameter, which must be entirely within 80% to 125% boundaries. The width of the CI reflects, in part, the within-subject variability of the test and reference products. The limits of 90% CI for each pharmacokinetic parameter are as follows:

**AUC-ratio:** The 90% confidence interval for this measure of relative bioavailability should lie within a bioequivalence range of 80–125. If the therapeutic range is particularly narrow, the acceptance range may need to be reduced. A larger acceptance range may be acceptable in exceptional cases if justified clinically.

**C<sub>max</sub>-ratio:** In general the acceptance limit of 80–125 should be applied to the C<sub>max</sub>-ratio. However, this measure of relative bioavailability is inherently more variable than, for example, the AUC-ratio, and in certain cases a wider acceptance range (e.g. 75–133) may be acceptable. The range used must be defined prospectively and should be justified, taking into account safety and efficacy considerations. In exceptional cases, a simple requirement for the point estimate to fall within bioequivalence limits of 80–125 may be acceptable with appropriate justification in terms of safety and efficacy.

**t<sub>max</sub>-difference:** Statistical evaluation of t<sub>max</sub> makes sense only if there is a clinically relevant claim for rapid onset of action or concerns about adverse effects. The nonparametric 90% confidence interval for this measure of relative bioavailability should lie within a clinically relevant range.

The primary comparison of interest in a bioequivalence study is the ratio of average parameter data (AUC & C<sub>max</sub>) from the test and reference formulations rather than the difference between them. Log transformation of the data allows the general linear statistical model to draw inferences about the ratio of the two averages on the original scale. Log transformation thus achieves the general comparison based on the ratio rather than on the difference. Moreover, plasma concentration data, including AUC and C<sub>max</sub> tends to be skewed and their variances tend to increase with the mean. Log transformation corrects this situation and makes the variances independent of the mean. Further, the frequency
distribution skewed to the left, i.e., those with a long tail to the right is made symmetrical by log transformation. In case no suitable transformation is available, the non-parametric method should be used. T_{\text{max}} values being discrete, data on T_{\text{max}} should be analyzed using non-parametric methods.

A common misconception promoted by manufacturers is that the average values between the reference and test product can vary by -20/+25%, which could lead to large differences in efficacy between multisource products. In fact, when applying these statistical criteria to studies involving 20 to 40 subjects, generic products whose mean arithmetic bioavailability parameters differ by more than 5% to 10% from the reference product begin failing the CI requirement. The FDA’s Office of Generic Drugs has conducted two large surveys to quantify the differences between generic and brand-name products. The first conducted on 224 bioequivalence studies submitted in approved applications during 1985 and 1986 found an average difference in AUC measures between reference and generic products of 3.5%\textsuperscript{56}. The second, involving 127 bioequivalence studies submitted in 1997 found average differences of 3.47% for AUC and 4.29% for C_{\text{max}}\textsuperscript{57}.

2.2.5. Need for bioequivalence study

2.2.5.1. Bioequivalence for first entry products

BE studies may be useful during drug development and registration for a first entry product during the Investigational New Drug (IND) or New Drug Application (NDA) period to establish links between (i) early and late clinical trial formulations (ii) formulations used in clinical trial and stability studies, if different (iii) clinical trial formulations and to be marketed drug products (iv) other comparisons as appropriate. In each comparison, the new formulation or new method of manufacture is the test product and the prior formulation or method of manufacture is the reference product.
2.2.5.2. **Bioequivalence for interchangeable multi-source products**

BE studies are a critical component of Abbreviated New Drug Applications (ANDA). The purpose of these studies is to compare relative BA measures between a pharmaceutically equivalent multi-source test product and the corresponding reference pioneer product. The innovator product is termed as Reference Listed Drug (RLD). Together with the determination of pharmaceutical equivalence, demonstrating BE allows a regulatory conclusion of therapeutic equivalence and interchangeability between the test and reference product.\(^{19}\)

2.2.5.3. **Bioequivalence for post approval changes**

Generally specifications are adequate to assure product quality on the assumption that no important change occurs post-approval. In the presence of major changes in components and composition, and/or method of manufacture of a drug product after approval, BE may need to be re-demonstrated. For approved first-entry products, the drug product after the change should be compared to the drug product before change. For approved interchangeable multi-source products, the drug product after the change should be compared to the reference listed drug.

2.2.6. **Role of In-Vitro Studies**

Under certain circumstances, FDA may waive the requirement for *in vivo* bioequivalence and/or bioavailability studies\(^ {58}\). The high soluble and high permeable BCS Class 1 drugs of immediate release orally administered formulations are eligible for Biowaiver. The requirement for *in vivo* bioequivalence and/or bioavailability studies may be waived if data demonstrate that formulations are identical and bioavailability is self-evident, as it is for injectables, ophthalmic solutions, and oral solutions since they are already solutions and dissolution concerns are not relevant; or when, in the case of solid oral dosage forms (excluding enteric-coated or controlled-release [CR] products), the product has been shown to be effective for at least one indication in a Drug Efficacy Study Implementation notice or
is related or similar to such a product and has not been identified as having a known or potential bioequivalence problem. Drug products that are known or expected to have bioequivalence problems, and for which \textit{in vivo} bioequivalence studies are required, are listed in Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book)\textsuperscript{19}. In general, such drugs are critical dose/narrow therapeutic index (NTI) agents, poorly soluble, slowly soluble, administered as a high dose, poorly absorbed, and/or unstable in gastrointestinal (GI) fluids. The available data conclusively demonstrate that the drugs that have NTIs are more prone to bioequivalence problems; many clinicians are concerned that small changes in the bioavailability of the active ingredient may lead to significant changes in the efficacy or safety of the product\textsuperscript{59,61}. Gabapentin is a BCS Class 3 drug of high solubility and low permeability category. The FDA classified as AB rated dmg and having actual or potential bioequivalence issues. The drug that has been proven to meet the necessary bioequivalence requirements through \textit{in vivo} testing compared to a reference standard that is currently approved.

\section*{2.3 GENERIC DRUGS}

A generic drug is one that is made other than by the original developer of a drug or under its authority which having same active ingredient in same amount in similar dosage form of original drug. Once the patent period for an innovator/original drug expires, monopoly of the innovator comes to an end and generic drugs having the same formula as the innovator drug can be marketed at a much lower price. These drugs offer great advantage of being cheap, as their manufacturers have to bear approximately 1/10th cost in comparison to original registration studies. Prescribing generic drug products may be actually beneficial as there is no significant change in the quality of the patient care and it may be actually better as they may lead to significant cost saving\textsuperscript{62}. Many nations throughout the world have come to rely on low-cost, good-quality multi-source (generic) pharmaceutical products as means of providing lower healthcare costs without sacrificing important public health goals.
Chapter 2

For a drug to be marketed under a generic label in USA, the manufacturer must comply with FDA standards. In order to ensure its safety and effectiveness, a generic drug undergoes intensive testing. Generic drugs that have been tested and approved by the FDA to be therapeutically equivalent to brand name drugs are published in a guide that is updated monthly and is found in most pharmacies. The guide lists drugs classified as therapeutically equivalent to each other, and gives them an "A" rating. If the FDA does not consider a drug therapeutically equivalent, it is given a "B" rating. Most pharmacies purchase drugs with an "A" rating to dispense as generic.

2.3.1. Generic drug approval process

Pre-1984 the process for generic drug approval has evolved along with changes in federal drug law and regulations. Before enactment of the Food, Drug, and Cosmetic Act (FDCA) in 1938, significant regulatory barriers to generic competition in the market did not exist. Manufacturers of such products (e.g., codeine sulfate, phenobarbital) could formulate, manufacture and sell their products without submitting bioequivalence or efficacy data to the FDA. The 1938 Act established a "new drug" category, requiring manufacturers to document the safety of a product to the FDA and established a 60-day delay before marketing could proceed, absent FDA objection. Until 1962 generic versions of post-1938 drugs were marketed based on a "general recognition" of safety. Typically, this designation was based on a history of safe use of the innovator product. Such generic products were designated as "not new drugs."

Amendments to the FDCA in 1962 added requirements for "substantial evidence of both safety and efficacy, obtained in adequate and well-controlled studies," and affirmative FDA approval of the New Drug Application (NDA); these criteria also applied to generic drugs. These amendments also contained a provision for retroactive evaluations of pre-1962 drugs that had been recognized as safe. The Drug Efficacy Study Implementation (DESI) Review established expert panels to review data on all drugs marketed between 1938 and 1962 and to make recommendations on their efficacy. About 1,099 drugs were found to be ineffective and were taken off the market whereas 2,302 were found effective, with any questionable
claims removed from the label. About 7,000 drugs identical or similar to the drugs under review were relabeled or withdrawn from the market. The generic drugs will undergo Abbreviated New Drug Application (ANDA) process through Drug price Competition and patent Term Restoration Act in the drug approval.

2.3.1. Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act)

The dual purposes of the Hatch-Waxman Act were to encourage the development of new innovator drugs by extending patent rights and to establish procedures facilitating the approval of low-cost generic drugs. These amendments to the FDCA codified in statute an Abbreviated New Drug Application (ANDA) process for post-1962 drugs whereby a generic company could gain approval of its version of a drug without repeating the expensive and lengthy clinical trials used to establish safety and efficacy of the innovator drug [Drug Price Competition and Patent Term Restoration Act of 1984].\(^{64}\) Products approved under an ANDA must be pharmaceutical equivalents (i.e., have the same active ingredient(s), route of administration, dosage form, and strength) as the reference drug. They must also be bioequivalent and the manufacturer must supply other basic technical information related to manufacturing of the product that is normally required of an NDA [Federal Food, Drug and Cosmetic Act, section 505(j) (8)]. Generic drugs are pharmaceutical equivalents only with respect to their active ingredients. The binders, diluents, and excipients (filler) in the formulation, as well as the method of manufacture may vary.

2.3.2 Power of the generics

In 1975 approximately 9% of all prescription drugs dispensed in US were generic versions\(^{65}\). This figure rose to 20% in 1984 and 40% in 1991\(^{66}\). Today generic drug products are used to fill over 50% of all prescriptions and since they cost a fraction of the price of brand name drugs, the economic impact of FDA's generic drug program is profound. With this in mind the Office of Generic Drugs (OGD) continues working expeditiously to review and take
action on generic drug applications as quickly as possibly. Generic medicines should be promoted since it saves patient’s money and it improves financial status of health insurance. In order to promote the use of generic medicines, it is important to ensure stable supply and appropriate information provision for patients and medical professionals.

American Medical Association has extensive policy related to generic drugs use. These policies are:

• Support the ability of physicians to use either generic or brand name drugs.
• Encourage physicians to consider relative cost when making their decision.
• Recognize that only “A”-rated generic drugs are suitable for substitution.
• Suggest several steps that can be taken by physicians and pharmacists to avoid confusion among patients when generic substitution or switching among generic products occurs.

A pharmacist may legally fill a prescription in the United States with either the brand name or a generic without consulting either the patient or the physician. A prescription may not even be filled consistently with the same generic. To assure continuity for the patient, the physician should indicate on the prescription as ‘no substitutions’ or ‘Dispense As Written’ (DAW). Under current Food and Drug Administration (FDA) regulation, a patient may switch from the brand-name drug to a generic drug if the generic drug is shown to be bioequivalent to the brand-name drug based on bioequivalence testing (therapeutic equivalence evaluation).

2.3. Generic drug scandal and FDA reaction

In 1989 federal investigators implicated several generic industry officials in the conduct of fraud, obstruction of justice, and noncompliance with various manufacturing procedures. The investigations also revealed that several FDA employees had accepted illegal gratuities or other compensation in exchange for information and assistance that gave certain firms an advantage in the approval process. Investigators also discovered that 10 or more generic
companies had submitted fraudulent data related to bioequivalence, stability testing, and manufacturing protocols for some of their products. The FDA reacted to these findings by reorganizing its generic drug operations and conducting comprehensive inspections. FDA investigators reevaluated data from hundreds of generic drug applications. More than 2,550 samples of the top 30 prescribed generic drugs or about 30% of all generic drugs on the market were collected and laboratory-tested and the agency conducted intensive inspections of 36 of the largest generic drug firms and 12 contract laboratories. The agency determined that only 27 samples, or approximately 1% of those tested, did not comply with standards of potency, dissolution, content uniformity, product identification, moisture determination, or purity.

The FDA also tested 429 samples representing at least three different batches of the so-called narrow-therapeutic-range drugs that were currently marketed. These 24 drugs, made by 73 brand-name and generic drug manufacturers, were selected because of their potential for adverse reactions or therapeutic failure if they lacked bioequivalency. Only five of the samples (all aminophylline tablets) failed to meet United States Pharmacopoeia standards. None of the defects in the generic drugs were judged to pose a public health hazard.

The mechanism for protecting patients from inferior drug products is Therapeutic Inequivalence Action Coordinating Committee (TIACC) by FDA, located in Rockville, Md., which evaluates alleged cases of therapeutic inequivalence.

2.3.4. Therapeutic equivalence of generic products

One of the most valuable resources on therapeutic equivalence about generic products is the Orange Book. FDA classifies as therapeutically equivalent products that are approved as safe and effective, pharmaceutically equivalent, bioequivalent, adequately labeled, and manufactured in compliance with the FDA's Good Manufacturing Practice regulations.
For every multiple-source product, the Orange Book cites a letter code named Therapeutic Evaluation (TE) Code that indicates the FDA's evaluation regarding the therapeutic equivalence of the product relative to the reference innovator or brand-name product. These drugs are placed in one of two categories as follows:

Multisource products are rated "A" (therapeutically equivalent, with no known or suspected bioequivalence problems) or "B" (not considered at this time to be therapeutically equivalent, with documented or potential bioequivalence problems). Each of these categories contains subcategories based on the dosage form. Actual or potential bioequivalence problems have been resolved with adequate in vivo and/or in vitro evidence supporting bioequivalence. These are designated AB. Class AA drugs are those with no known potential or actual BE problems and interchangeable with other multi-source pharmaceutical equivalent products whereas Class BX products are not interchangeable. Most new generic products are defined as having “potential” problems until data is submitted to establish their bioequivalence. This gives provision of immediate switch to available generic products which are equivalent to RLD by healthcare provider when required by the patients.

Despite the strict standards imposed by the FDA for approval of generic drugs, their enforcement of these standards and assurance of quality of generic products, a number of misconceptions about generic drugs still persist among physicians and patients. Medical profession has also realized the problem of wide variations in the therapeutic effectiveness of various marketed brands of oral formulations containing the same active ingredient in equal amount. A number of patients with a history of good results on brand name drugs observed difficulties when a generic was substituted to decrease the cost of therapy.

The mechanism for protecting patients from inferior drug products is Therapeutic Inequivalency Action Coordinating Committee (TIACC) by FDA, located in Rockville, Md., which evaluates alleged cases of therapeutic inequivalence. These evaluations are difficult because many therapeutic failures are actually the result of a worsening of the patient's disease rather than therapeutic inequivalence. TIACC notes that several published reports of
therapeutic inequivalence could not be supported when the cases were reviewed in detail. The committee has contended that there is often a bias present suggesting that the "generic drug" is inferior and thus, data may be intentionally or unintentionally omitted from a report.80

2.3.5. Status of Reference Product for generic drug approval

Most drug products on the market today have been subjected to bioequivalence assessment at various stages in their development. As is well known, generic drug products require the demonstration of bioequivalence to the relevant innovator product for regulatory approval. What is perhaps less well known is that most innovator products too require some form of bioequivalence testing. New drugs typically undergo pharmacokinetic dose-proportionality studies, drug-drug and drug-food interaction studies, all of which use the bioequivalence concept. The site of development and production of the drug product could be changed. Most importantly, when the innovator formulation to be marketed is different from the formulation used previously in pivotal efficacy trials, as is often the case, bioequivalence of the marketed formulation to the clinical trial formulation must be shown. In this sense, many innovator drug products on the market are in fact 'generic copies' of the clinical trial formulation for which therapeutic efficacy and safety had been shown in patients.74 The details of reference product requirements for new generic drug approval in WHO, FDA and CDSCO guidelines are discussed.

2.3.5.1. WHO guideline (Comparator product)

The reference product in WHO BA/BE study is comparator product.75 The innovator pharmaceutical product is usually the most logical comparator product for a multisource pharmaceutical product because its quality, safety and efficacy should have been well assessed and documented in premarketing studies and postmarketing monitoring schemes. For some pharmaceutical products however, an innovator product cannot be identified; and in some cases no innovator product is available in the market. A generic pharmaceutical
product should not be used as a comparator as long as an innovator pharmaceutical product is available as this could lead to progressively less reliable similarity of future multisource products and potentially to a lack of interchangeability with the innovator. The selection of the comparator product is usually made at the national level by the drug regulatory authority.

In principle, a national drug regulatory authority has the following options which are listed in order of preference:

1. To choose the innovator product for which quality, safety and efficacy has been established; if this product has been granted a national marketing authorization ("nationally authorized innovator") or

2. To choose the WHO comparator product (for which marketing authorization has been granted, on the basis of quality, safety and efficacy) ("WHO comparator product"). The primary manufacturing site is indicated in the WHO comparator list (6), and the comparator is to be purchased in that country or

3. To choose the innovator product for which a marketing authorization has been granted in a well-regulated country (ICH or associated country) on the basis of quality, safety and efficacy ("ICH et al., innovator") and which is to be purchased from that market or

4. In the case where no innovator product can be identified - within the context of (1)-(3) above, the choice of the comparator must be made carefully and must be comprehensively justified by the applicant. The most important selection criteria in order of preference are:

   - Approval in ICH- and associated countries;
   - "Prequalified" by WHO;
   - Extensive documented use in clinical trials reported in peer reviewed scientific journals;
   - Long and unproblematic period of post market surveillance ("well selected comparator"). Additionally, "well selected comparators" must conform to compendial quality standards, where these exist.
Chapter 2

A product that has been approved based on comparison with a nondomestic comparator product may or may not be interchangeable with currently marketed domestic products. In the context of regional harmonization efforts, it may be advantageous to establish a regional comparator product, for which quality, safety and efficacy has been established, in order to increase access to medicines. The choice of comparator product should be justified by the applicant. The country of origin of the comparator product should be reported together with lot number and expiry date.

2.3.5.2. FDA guideline (Reference Listed Drug)

The reference product in FDA BA/BE study is Reference Listed Drug (RLD). The RLD is an approved drug product to which new generic versions are compared to show that they are bioequivalent. A drug company seeking approval to market a generic equivalent must refer to the Reference Listed Drug in its Abbreviated New Drug Application (ANDA). By designating a single reference listed drug as the standard to which all generic versions must be shown to be bioequivalent, FDA hopes to avoid possible significant variations among generic drugs and their brand name counterpart. The status of Reference Listed Drug to Gabapentin from the Electronic Orange Book maintained by FDA is shown in Table 3:

Table 3: The details of RLDs to Gabapentin molecule

<table>
<thead>
<tr>
<th>TE Code</th>
<th>RLD</th>
<th>Active Ingredient</th>
<th>Dosage Form</th>
<th>Strength</th>
<th>Proprietary Name</th>
<th>Applicant</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB</td>
<td>Yes</td>
<td>GABAPENTIN</td>
<td>TABLET; ORAL</td>
<td>800MG</td>
<td>NEURONTIN</td>
<td>PFIZER PHARMS</td>
</tr>
<tr>
<td>AB</td>
<td>Yes</td>
<td>GABAPENTIN</td>
<td>CAPSULE; ORAL</td>
<td>400MG</td>
<td>NEURONTIN</td>
<td>PFIZER PHARMS</td>
</tr>
<tr>
<td>AA</td>
<td>Yes</td>
<td>GABAPENTIN</td>
<td>SOLUTION; ORAL</td>
<td>250MG/5 ML</td>
<td>NEURONTIN</td>
<td>PARKE DAVIS</td>
</tr>
<tr>
<td>BX</td>
<td>Yes</td>
<td>GABAPENTIN</td>
<td>TABLET; ORAL</td>
<td>300MG</td>
<td>GRALISE</td>
<td>ABBOTT PRODS</td>
</tr>
<tr>
<td>BX</td>
<td>Yes</td>
<td>GABAPENTIN</td>
<td>TABLET; ORAL</td>
<td>600MG</td>
<td>GRALISE</td>
<td>ABBOTT PRODS</td>
</tr>
<tr>
<td>-</td>
<td>Yes</td>
<td>GABAPENTIN ENACARBIL</td>
<td>TABLET, EXTENDED RELEASE; ORAL</td>
<td>600MG</td>
<td>HORIZANT</td>
<td>GLAXO GRP LTD</td>
</tr>
</tbody>
</table>
2.3.5.3. CDSCO guidelines (Designated Reference Product)

The reference product in India—CDSCO BA/BE study is Designated Reference Product (DRP). The reference product is a pharmaceutical product which is identified by the Licensing Authority as "Designated Reference Product" and contains the same active ingredients as the new drug. The Designated Reference will normally be the global innovator's product. An applicant seeking approval to market a generic equivalent must refer to the Designated Reference Product to which all generic versions and must be shown to be bioequivalent. For subsequent new drug applications in India, the Licensing Authority may however, approve another Indian product as Designated Reference Product.

2.3.6. Formulation availability in India

Indian markets are flooded with huge number of generic formulations available for every drug molecule, with significant pricing difference between the different brands of the same formulation. This apart from creating confusion among innocent consumers, often, allows them to be misled by unfair traders. Price difference between different brands of products were found to vary up to the extent of 7% to 81%.

The global innovator drug Neurontin (solid dosage form) containing Gabapentin was launched by Pfizer Company, approved for partial seizure in 1993 by FDA and marketed in USA. In 2004, patent period for Neurontin expired. Pfizer produced its own generic form along with other pharmaceutical companies in USA and it launched its product in India in the year 2000. In India, Sun Pharma and Intas Pharma launched Gabapentin (generic to Neurontin) formulation in year 1998. Currently, Neurontin innovator product of Gabapentin is unavailable in Indian market and the reason is unknown. Some of the available generic Gabapentin formulations (300 mg IR capsule form) in India are listed in Table 4.
2.4. DRUG INTERCHANGEABILITY

To ensure drug interchangeability according to the WHO, the multisource (generic) product must be therapeutically equivalent to the comparator product. For therapeutic equivalence the \textit{in vivo} and \textit{in vitro} studies were required.

The \textit{in vivo} studies include pharmacokinetic studies, pharmacodynamic studies and comparative clinical trials. Direct practical demonstration of therapeutic equivalence in a clinical study usually requires large numbers of patients. Such studies in humans can be financially daunting, are often unnecessary and may be unethical. For these reasons, the science of bioequivalence testing has been developed over the last 40 years. According to the tenets of this science, therapeutic equivalence can be assured when the multisource product is both pharmaceutically equivalent/alternative and bioequivalent.\textsuperscript{75} Assuming that in the same subject an essentially similar plasma concentration time course will result in essentially similar concentrations at the site(s) of action and thus an essentially similar therapeutic outcome, pharmacokinetic data may be used instead of therapeutic results.

In selected cases, \textit{in vitro} comparison of dissolution profile of the multisource product with that of the comparator product or dissolution studies may be sufficient to provide indication of equivalence.
According to the WHO guideline, it should be noted that the concept of interchangeability includes the equivalence of the dosage form as well as of the indications and instructions for use. The guideline also points out that all the pharmaceutical products, including multisource products, should be used in a country only after approval by the drug regulatory authority. The national health and drug regulatory authorities should ensure that all pharmaceutical products subject to their control conform to acceptable standards of safety, efficacy and quality, and that all premises and practices employed in the manufacture, storage and distribution of these products comply with good manufacturing practice (GMP) standards so as to ensure the continued conformity of the products with these requirements until they are delivered to the end-user.75

In general drug interchangeability in clinical practice includes drug prescribability or drug switchability. Drug prescribability refers to the situation where a patient is treated with either an innovator product or any bioequivalent generic product. Drug switchability refers to the situation where the innovator product prescribed is switched on to a generic drug product. The following situations where the drug interchangeability (switchability) can take place:

- Preference to cheap generic drugs over prescribed costlier drug for cost saving or reducing healthcare budget.
- Unavailability of prescribed drug in the pharmacy.
- Unavailability of prescribed drug in the hospital formulary and/or Insurance plan.

The drug interchangeability is very important for patients. Several studies have reported that over 90% of people with epilepsy in developing countries do not receive appropriate treatment for their condition, a phenomenon known as the treatment gap and reported that the maximum cause accounted for cost of treatment (90%), traditional treatment (82%), inadequate skilled manpower (76%), superstitions and cultural beliefs (65%), unavailability of drugs (44%), and long distance to health facilities (19%).78 The major cause of treatment gap is cost of drug and also true for other disease conditions.
Also, while switching from a branded to the generic formulation, lower cost cannot be used as safe criteria, since the major end-point in treating epileptic patients is complete seizure control with tolerable side effects. The compulsory generic substitution of antiepileptic drugs may lead to adverse effects in epileptic patients because of seizure recurrence or increased toxicity. The recent survey report indicated that there is a potential problem with generic substitution of antiepileptic drugs and it was found that 67.8% among 301 neurologists reported breakthrough seizures after switch from a brand to generic antiepileptic drugs and 56% reported increased side effects after switch to generic drugs. The involved drugs include phenytoin, valproic acid, lamotrigene, carbamazepine, and clonazepam. All these drugs are the medication class of narrow therapeutic index drugs and apart from the drug properties, disease pathological conditions were also involved in causing breakthrough seizures in drug substitution. Like this, the information about breakthrough seizure in Gabapentin substitution is unavailable, however, presently research on gabapentin mostly focused on condition other than epilepsy because of adjuvant therapy in epilepsy worldwide. The main approved clinical use is neuropathic pain and other unapproved use in neurology and psychiatry is common.

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 where small differences in the amount of drug in the bloodstream can make a very large difference in the dmg's effectiveness, generic drugs are often not substituted for trade-name drugs, although bioequivalent generic products are available. Digoxin and theophylline 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. Thus, if a doctor specifies a trade-name drug on the prescription and the consumer wants an equivalent generic version, the consumer or pharmacist should discuss the matter with the doctor.

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, used to treat people with heart failure, is an example.
Switching from the trade-name version of digoxin to a generic product may cause problems because the two versions may not be sufficiently bioequivalent. However, some generic versions of digoxin have been certified as bioequivalent by the FDA. Pharmacists and doctors can answer questions about which generic drugs are interchangeable for their trade-name counterparts and which are not. The generic drug substitution may not be appropriate for certain category of the drugs as indicated in Table 5."

**Table 5: When generic substitution may not be appropriate**

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Examples</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs on the market before the 1938 Federal Food, Drug, and Cosmetic Act</td>
<td>Despite efforts by the FDA, some brands of thyroid hormone replacement products are still not bioequivalent</td>
<td>Pre-1938 drugs are exempt from generic drug requirements, but only a few of these are still prescribed. Switching among different versions is unwise because no standards are available by which to compare them. Exercise caution when switching brands.</td>
</tr>
<tr>
<td>Drugs with little difference between a toxic dose and an effective dose (a narrow margin of safety)</td>
<td>Anticonvulsants such as phenytoin, carbamazepine, and valproate; digoxin (for heart failure and a very rapid heart rate); and the anticoagulant warfarin</td>
<td>The margin of safety is relatively small. Too little drug may not work, and too much drug may cause side effects.</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>Reserpine and reserpine plus polythiazide</td>
<td>Generic versions are not bioequivalent to trade-name drugs.</td>
</tr>
<tr>
<td>Antiasthmatic drugs taken by mouth</td>
<td>Theophylline, dyphylline, and some brands of aminophylline</td>
<td>Different versions are generally not bioequivalent. If one version is working, it should not be interchanged for another unless absolutely necessary.</td>
</tr>
<tr>
<td>Corticosteroid creams, lotions, and ointments</td>
<td>Alclometasone, amcinonide, betamethasone, clocortolone, desonide, desoximetasone, dexamethasone, diflorasone, fluocinolone, fluocinonide, flurandrenolide, fluticasone, halcinonide, halobetasol, hydrocortisone, mometasone, and triamcinolone</td>
<td>These products are standardized by tests of skin response, and many have been rated as bioequivalent by the FDA. But response varies, and different drug vehicles (creams, ointments, gels) can affect product potency. Response may be unpredictable. So, if one version is effective, it should not be interchanged for another.</td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>Dexamethasone,</td>
<td>Many generic versions are not</td>
</tr>
<tr>
<td>Category</td>
<td>Example Drugs</td>
<td>Notes</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>tablets</td>
<td>triamcinolone, and others bioequivalent to trade-name drugs and should not be freely interchanged for them.</td>
<td></td>
</tr>
<tr>
<td>Hormones</td>
<td>Esterified estrogen (estrogen replacement therapy in postmenopausal women), some brands of medroxyprogesterone, and most generic brands of methyltestosterone</td>
<td>The two brands of esterified estrogen are not bioequivalent. Hormones are usually taken in small doses, so differences in brands could produce major swings in response.</td>
</tr>
<tr>
<td>Antihyperglycemic drugs</td>
<td>Glyburide (for type 2 diabetes) One version of glyburide, Diabeta, may not be interchanged for any other. All other versions are considered interchangeable.</td>
<td></td>
</tr>
<tr>
<td>Drugs to control gout</td>
<td>Colchicine Generic versions of individual drugs are not bioequivalent to one another.</td>
<td></td>
</tr>
<tr>
<td>Antipsychotic drugs</td>
<td>Chlorpromazine tablets Generic versions are not bioequivalent to the trade-name version.</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>A few brands of amitriptyline and one brand of amitriptyline plus perphenazine Not all versions are interchangeable. A pharmacist can advise whether the FDA considers a particular generic drug bioequivalent to the trade-name drug</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>Most long-acting potassium replacement products in tablet form Long-acting potassium products in capsule (not tablet) form are considered bioequivalent and may be interchanged</td>
<td></td>
</tr>
<tr>
<td>Other drugs</td>
<td>Fluoxymesterone, some brands of promethazine tablets and suppositories, chloramphenicol capsules, and clozapine Generic versions may not bioequivalent. Although any version can be effective, versions should not be interchanged.</td>
<td></td>
</tr>
</tbody>
</table>

The substitution of a generic drug can sometimes cause other problems for the consumer. A doctor may write a prescription for a trade-name product and discuss the trade-name product with the consumer. If a pharmacist dispenses an equivalent generic product and the label does not also list the reference (trade-name product), the consumer may not know how the generic product relates to the drug the doctor prescribed. To prevent this confusion, pharmacists should include the reference trade name on the label when a generic product is substituted.

Many developing countries do not have an effective means of monitoring the quality of generic drug products in the market. This results in widespread distribution of substandard...
and/or counterfeit drug products. Therefore medical profession has realized the problem of wide variations in the therapeutic effectiveness of various brands of oral formulations containing the same active ingredient in equal amounts. For example, lack of bioequivalence among different brands has been well documented for digoxin, phenobarbital, prednisolone, tolbutamide, diclofenac sodium and aspirin formulations.\textsuperscript{9-14} Some of the counterfeit drugs detected in the market\textsuperscript{84} are shown in Table 6.

Table 6: Report of counterfeit drugs detected in the market

<table>
<thead>
<tr>
<th>Counterfeit medicine</th>
<th>Country/Year</th>
<th>Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-diabetic traditional medicine (used to lower blood</td>
<td>China, 2009</td>
<td>Contained six times the normal dose of glibenclamide (two people died,</td>
</tr>
<tr>
<td>sugar)</td>
<td></td>
<td>nine people hospitalized)</td>
</tr>
<tr>
<td>Metakelfin (antimalarial)</td>
<td>United Republic of Tanzania,</td>
<td>Detected in 40 pharmacies: lacked sufficient active ingredient</td>
</tr>
<tr>
<td>2009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viagra &amp; Cialis (for erectile dysfunction)</td>
<td>Thailand, 2008</td>
<td>Smuggled into Thailand from an unknown source of an unknown country</td>
</tr>
<tr>
<td>Xenical (for fighting obesity)</td>
<td>United States of America, 2007</td>
<td>Contained no active ingredients and sold via Internet sites operated outside the USA</td>
</tr>
<tr>
<td>Zyprexa (for treating bipolar disorder and schizophrenia)</td>
<td>United Kingdom, 2007</td>
<td>Detected in the legal supply chain: lacked sufficient active ingredient</td>
</tr>
<tr>
<td>Lipitor (for lowering cholesterol)</td>
<td>United Kingdom, 2006</td>
<td>Detected in the legal supply chain: lacked sufficient active ingredient</td>
</tr>
</tbody>
</table>

Similar reports from the developing countries are lacking. This may be due to the fact that the transparency of drug regulations is still not stringent in developed countries. Truly they have minimal or completely lack the resources to identify the flaws and therefore unavailable to public, however India has data.
The "Report on Countrywide Survey for Spurious Drugs" is published in 2009 by CDSCO on behalf of Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India. The survey report is produced to fulfill the requirements prescribed in the Drugs & Cosmetics Rules-1945 for standards of drugs produced and/or marketed in India and contributes in control of quality of the medicinal products. The quality of Drug formulations has been of prime concern at national as well as international level. Circulation of spurious drug can lead to grave and adverse consequences on both consumers (patients) and genuine manufacturers. According to the report received from various State Drug Controllers, the extent of circulation of spurious drug in Indian retail market is about 0.3%. However, the media often magnifies it in a sensational manner, between 10-25% which is mostly unverified. Indian Pharma Industry expressed displeasure over the repeated projection of Indian Pharma Industry as major producers of spurious drugs in the world.

Clinical studies comparing innovator and generic drugs are rarely published, and studies comparing one generic product with another are almost never performed. However, in 1970s it was recognized that differences in the formulation of products containing the same amount of active ingredient could result in significant differences in bioavailability and several cases of therapeutic inequivalence involving generic products were reported.

Overall, from the available literature and knowledge it was found that Gabapentin is approved for Partial seizure and Postherpetic neuralgia in human and it has 2-3 hr time to maximum absorption concentration and 5-7 hr half-life after oral absorption. It is a BCS Class III of high solubility and low permeability drug. It has saturation absorption kinetics through L-amino acid carrier transport mechanism and linear steady state plasma concentration with therapeutic dose but the absolute BA will decrease because of dose amount. Titration of dose is dependent on patient tolerability and efficacy experience. Titration of dose is necessary in renal failure patients. It is not an NTI drug and there is no need for TDM and is not a highly variable drug and not metabolized in body and the unchanged form will be eliminated by renal route. For the drug interchangeability, the in-vivo oral bioavailability studies with the in-vitro dissolution profile can fulfill the assessment of
therapeutic equivalence for Gabapentin 300 mg capsule (immediate release formulation) of different manufacturers.