SUMMARY
AND
CONCLUSIONS
Medical profession has realized the problem of wide variations in the therapeutic effectiveness of various marketed brands of oral formulations containing the same active ingredient in equal amounts.

According to the current regulatory guidelines (USFDA; DCGI and EMEA), two products are generally considered to be bioequivalent if they yield comparable bioavailability when administered to the same individuals in the same dose and under similar conditions. The formulations thus deemed to be bioequivalent are therapeutically interchangeable.

In the present study we evaluated the steady-state bioequivalence of three marketed brands of sodium valproate available in India in healthy, male, adult, human subjects under fasting conditions.

The clinical study was carried out in accordance with ICH Good Clinical Practices. The study protocol and the informed consent form were approved by the Jamia Hamdard Institutional Review Board. Each of the subjects was required to understand and give his consent to participate in the study by signing the informed consent form. The signed original copy was retained and a copy was given to each study subject for record. The washout period maintained between the each period was of seven days.

Bioequivalence was assessed by measuring the pharmacokinetic parameters namely $C_{\text{max(ss)}}$, $T_{\text{max(ss)}}$, $AUC_{0-12(ss)}$, $C_{\text{min(ss)}}$, $C_{\text{avg(ss)}}$ and percentage fluctuation for sodium valproate 500 mg enteric coated tablets.

Blood samples were collected within 2 minutes of the specified time as per study design. Intravenous indwelling cannula was kept in situ as long as possible, otherwise an alternative method of collecting by fresh clean veni punctures using standard disposable sterilized syringe and a needle was used. After collection, blood samples were centrifuged as per the processing method to separate plasma. All plasma samples were stored in suitably labeled polypropylene tubes at -70°C till analysis.
A validated method in terms of selectivity, linearity, sensitivity, accuracy and precision was used for the estimation of diltiazem in plasma. The standard curve was linear & coefficient of co-relation was found to be greater than 0.99 throughout the study.

The bioequivalence criteria used were ratios of LSM of log transformed data for $C_{\text{max}(ss)}$ and $\text{AUC}_{0-t}(ss)$ at 90% confidence interval range of 90-111% for $C_{\text{max}(ss)}$ and 80-125% for $\text{AUC}_{ss0-t}(ss)$, as per the narrow therapeutic index drugs.

The following conclusions were drawn from the study

- Both the test products were bioequivalent to the reference product when the US FDA criteria (confidence interval limits 80-125%) for narrow therapeutic index drugs was applied. However this criterion does not differentiate a wide safety margin drug range from a narrow therapeutic drug range.

- Product B (Epilex®) was bioequivalent to Product R (Valparin®) when the confidence interval limits were tightened (90-111%) for $C_{\text{max}(ss)}$. Thus, only Epilex® can be substituted safely for Valparin® by the physicians and the pharmacist.

- The patient should always be informed about the switch by the physician and asked to be vigilant and immediately report in case of any changes observed in terms of adverse effects or increase in the seizure frequency.

- Although the generics substitution in these conditions may produce considerable saving, these savings should not be offset by increase in the hospitalization, nor the patients therapeutic stability should be compromised.

- The overall international scenario for criteria for bioequivalence of narrow therapeutic drugs is complicated and varies from country to country. The US guidelines require that although the acceptance criteria are similar to the wide margin drugs, the manufacturers should approach the CDER for an appropriate review. Thus, clearly there is no uniform guidance for the NTI drugs.