EDITORIAL

Prospects of Drug Bioequivalence Studies in Pakistan

S. Khaqan Hasan

A patented drug becomes generic after losing patent protection and it is estimated that drugs worth US$ 75 billion would become unpatented in 2012 thus creating a huge market for generic drugs.[1] The generic drugs can then be manufactured by any pharmaceutical firm other than the original patentee company and developing countries like India and China are manufacturing now many generic drugs. It is, however, necessary to prove that produced brand of the generic drug has the same quality, safety and efficacy as the original (originator's/ comparator's) drug by carrying out Bioavailability/ Bioequivalence (BA/BE) studies of the drug. Moreover, U.S.A is outsourcing drug related work worth US$ 20 billion and work worth US$ 3 billion is expected to go to China, India and other developing countries[1] and Pakistan could get a share of this market by developing BA/BE facilities with in the country.

This need has led to the rapid creation of the facilities for BA/BE studies of drugs in many developing countries like China, India, Philippines, Malaysia, Indonesia, Singapore, Jordan, Turkey and Pakistan.

Starting from scratch at independence, the pharmaceutical industry in Pakistan has grown steadily to the stage where Pakistan is exporting drugs to more than sixty countries.[2] These countries include Central Asian Republics, Russia, Sri Lanka, Philippines, Vietnam and African countries.[3] The exports of pharmaceutical products from Pakistan are increasing every year as Pakistan exported drugs worth U.S. $ 164 million in 2010[1] compared to US$ 85 million in 2007.[3]

There are 22 international units and 380 registered national pharmaceutical units with total worth of about US$ 1.9 billion, in Pakistan.[3] The pharmaceutical industry has the potential to export drugs worth US$ 600 million but our exports are still meager compared to India which exports drugs worth US$ 20 billion now.[2]

Our pharmaceutical companies could enhance export to achieve their full potential but suffer from the handicap that most of the importing countries need Bioavailability (BA) / Bioequivalence (BE) studies on drugs before allowing their imports from Pakistan.

Due to the lack of proper facilities, our drug firms need to send their products to centers in Singapore, Malaysia, Jordan and India for BA/BE studies requiring significant expenditure of foreign exchange before exporting their products.

In addition, World Health Organization (WHO) recommends use of fixed dose combination (FDC's) of only proven bioavailability for the treatment of tuberculosis.[4]

Drug Regulatory Authorities in Pakistan also may need these facilities in future for registration of drugs and checking substandard and counterfeit drugs.

The above needs have led to the establishment of the facilities for BA/BE studies in Pakistan both in public and private sectors. In public sectors, these include Center for Bioequivalence Studies and Bioassay Research (CSBR), University of Karachi, Bioequivalence Study Center at University of Veterinary and Animal Sciences, Lahore, Department of Pharmacy, The Islamia University of Bahawalpur and recently established Institute of Pharmaceutical and Environmental Research (IPER) at Dow University of Health Sciences (DUHS), Karachi. In private sector, Metrics Research, Karachi, Pharma Professional Services, Karachi and Pharma Dynamics at Karachi are providing BA/BE services in Pakistan.

The requirement for establishment of these centers for BA/BE studies are very stringent as attraction of clinical research as lucrative business could result in mushrooming of non-regulated centers in private sector leading to the abuse of volunteers and non-scrupulous work.

Both in vitro (outside the body) and in vivo (inside the body) studies are done to determine bioequivalence between two products such as commercially available brand product and a potential, to-be-marketed, generic product. In vitro studies are conducted in the laboratory according to the standard procedures following British (B.P), United States (U.S.P) or European pharmacopoeias including the needed disintegration, disassociation and hardness testing of the drug formulations.

Correspondence: Dr. S. Khaqan Hasan, Director, Institute of Pharmaceutical and Environmental Research, Dow University of Health Sciences, Ojha Campus, Karachi, Pakistan.

Email: sk.hasan@duhs.edu.pk

In vivo studies are performed by administration of the test and reference formulation of the drug, each as a single dose to normal healthy volunteers in an open label crossover procedure with randomization for treatment sequence and allowance for adequate washes between the two doses under strict regulations.[5] Trials must be approved by an Independent Ethics Committee (IEC) (or equivalent) before conducting the study. Various recommended regulations and guidelines like Helsinki declaration,[6] Good Clinical Practice (GCP),[7] Good Laboratory Practice (GLP)[8], International Conference on Harmonization (ICH)[9] guidelines and WHO recommendations [5] need to be followed.

These studies are done under the supervision of qualified medical staff. The healthy volunteers are selected after taking their medical histories and performing physical check-ups. Diagnostic facilities are needed for hematological, biochemical and other required laboratory evaluations. Most of the studies need to keep 24 volunteers for 24-48 hours for observation and sampling.

The blood samples are collected from the volunteers for a specific period after each dose and plasma is separated from the samples. Assay of the samples yields plasma concentration time curves for the drug from which pharmacokinetic variables are calculated and compared by standard statistical methods. The resulting pharmacokinetic data and associated statistical analysis are examined according to a set of predetermined criteria to confirm or refute that drug delivery and disposition are equivalent after administration of the test and reference formulation.

In case of an adverse reaction, facilities are needed for treatment in an emergency and for intensive care in a nearby hospital.

Conformation to various international guidelines and regulations, as mentioned above, necessitates establishment of following facilities at a BA/BE study Centre.

1. Office of Research, Innovation and Commercialization
2. Ethics Committee/ Institutional Review Board
3. Volunteer Recruitment Department
4. Screening area for selection of Healthy Volunteers
5. Diagnostic facility for checking the health of volunteers
6. Arrangement for housing volunteers `during study period
7. Laboratory for analysis of drug concentration in collected samples from volunteers
8. Hospitals for treatment of volunteer in case of severe adverse reaction to the administered.
9. Clinical Trial Unit

Although various BA/BE study centers in Pakistan have managed access to above facilities but none of the centers has all the above facilities under one roof or in close proximity.

A medical university is the best place to establish a center for carrying out BA/BE studies and DUHS has established required facilities at its Campus in Karachi for studies.

1. Office of Research, Innovation and Commercialization (Department of Research)

This office not only provides the registration of all the research studies, but also provides the data analysis, report writings and dissemination of research outcomes through publication of university scientific journal; namely Journal of Dow University of Health Sciences, abstracts books and organizing Research Days.

2. Institutional Review Board (IRB)

It allows BA/BE studies and clinical trials at DUHS only after an ethical review.

3. Screening Area

The volunteers are screened in this area to select healthy volunteers.

4. Dow Diagnostic Reference and Research Laboratory (DDRRL)

This laboratory has state-of-the-art equipment for diagnostic tests in chemical pathology, histopathology, hematology, microbiological and molecular pathology sections with associated Radiology laboratory and an animal house. It is fully equipped to carry out diagnostic tests on the volunteers.

5. Volunteer Health Care Facility

This facility could house 26 volunteers in 13 rooms with attached toilets, each containing two hospital beds with accessories, under the supervision of medical doctors and nursing staff. The facility contains dining and entertainment areas, reception, pharmacy, emergency room and offices for staff.

6. Bio Analytical Laboratory

This laboratory is equipped for pharmacokinetic studies of the administered drugs. It is located within the Institute of Pharmaceutical and Environmental Research (IPER) and has a highly qualified staff (M.Sc. (4) and Ph.D. (1) chemists) for bio analysis. In BA/BE studies, it is necessary to measure a very little amount of the intact drug in small volumes of body fluids, therefore, very sensitive analytical techniques like high performance liquid, chromatography (HPLC), UV-visible Spectrophotometry are used. This laboratory is equipped with HPLC, UV-Visible Spectrophotometer, gas chromatograph and other supporting laboratory equipment for determination of the intact drug in the blood plasma samples of the volunteers. The equipment

in this laboratory could do In vitro testing of the drug according to international standards (B.P, U.S.P, Eu. P) and for checking quality and purity of drugs. Staff and equipment in other laboratories (pharmaceutical, environment, food) in IPER also provide support for bio analytical work.

7. Hospital (500 Bed)

This hospital is located in close proximity of Volunteer Health Care Facility and a volunteer could be transferred immediately with an available ambulance in case of an adverse reaction to the Intensive Care Units in this hospital.

8. Clinical Trial Unit (CTU)

This unit coordinates clinical trials at DUHS. The clinical trials in phase I to check safety of a drug need the same facilities as for BA/BE studies and thus facilities at DUHS could also be used for Phase I trials.

Dow University is thus unique in Pakistan to provide one window services of international standards at its complex of above facilities in close proximity at one location to the pharmaceutical industries for BA/BE studies of the drugs.

For many years, the menace of substandard, spurious, fake and counterfeit is causing lot of suffering to the people in Pakistan resulting in the prolonged illness and even deaths of the patients. This menace is spreading and increasing every year without proper controls.

It has been estimated by World Health Organization (WHO) that, Pakistanis spend 77 percent of their budgets for health on the medicines, 50% which are fake or unfit for human consumption. About 40 to 50 percent of available medicines in Pakistan are counterfeit and our country is ranked 13th in the world for counterfeit drugs. Counterfeit and substandard drugs are rampant in urban and even more in rural areas.[10]

To improve this situation, it is necessary that all drug formulations in use should be tested for their quality according to the international standards both in vitro and in vivo for Bioavailability and Bioequivalence (BA/BE) studies. It should also be mandatory for public sector hospitals to get the drugs from suppliers, tested (in vitro), before making bulk or expensive purchases.

Although, there is Central Drugs Laboratory in Public Sector in Karachi but there is a need of more state-of-the-art drug testing laboratories in Pakistan to control this menace.

The drug testing equipment at IPER fulfill this need for drug testing and checking fake, spurious and counterfeit drugs.

Utilization of the created BA/BE facilities in Pakistan specially at DUHS would provide an opportunity in Pakistan to get a fair share of above market and to provide intellectual, knowledge based value added services in the medical sector not only at national but also at international level.

REFERENCES

1 Overview of the Indian CRO Market. (http://blogs.veedacr. com/List/Posts/Post.aspx?ID=335)

2 Pharma industry seeks government action against fake drugs. The Express Tribune February22, 2011 [Accessed January 04, 2013]. Available from: (http://tribune.com.pk/story/121892/pharma-industry-seeks-government-action-against-fake-drugs/).

3 Pharma exports to touch U.S. $ 600m by 2010: exporters. Daily times. Site Edition June 30, 2007 [Accessed January 04, 2013]. Available from: (http://www.dailytimes.com.pk/default.asp?page=2007%5C06%5C30%5Cstory_30-6-2007_pg5_2)

4 Ponchagnula R, Agarwal S, Kaur KJ, Singh I, Kaul, CL. Evaluation of rifampicin bioequivalence in fixed dose combinations using the WHO/ IUATLD recommendation protocol Int. J Tuber Lung Dis 2000; 4: 1169-72.

5 World Health Organization: additional guidance for organizations performing in vivo bioequivalence studies. WHO technical Report service, No937, 2006. [Accessed March 31,2011] Available From: (http://apps.who.int/prequal/info_general/documents/TRS937/WHO_TRS_937__annex9_eng.pdf)

6 World Medical Association Declaration of Helsinki Ethical Principles for medical research involving human subjects. Adopted by the 18th WMA General Assembly Helsinki Finland, June 1964 and amended by the 59th WMA General Assembly, Seoul, October 2008 Available from: http://www.wma.net/en/30pulications/10policies/b3/17c.pdf

7 Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. Geneva, World Health Organization, 1995 (WHO technical Services Report No.850): 90-137.

8 Good Laboratory Practices (GLP) Quality practices for regulated nonclinical research and development. Geneva/World Bank/WHO, Special Program for Research and Training in Tropical Disease (TDR), 2001.

9 International Conference on Harmonization (ICH) Guidelines. Tripartite Harmonization Guidelines for Good Clinical Practice, step 4, Geneva, ICH Secretariat (IFPMA), 1996. Available from: http://www.ich.org /fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf

10 40% of all medicines in Pakistan are fake. Daily times, March 09, 2006. Available from: http://www.dailytimes.com.pk/default.asp?page=2006\03\09\story_9-3-2006_pg7_60