radionuclides origin and abundance on different environmental matrices. Following, potential applications on environmental studies will be presented, and, finally, results obtained on several project developed by the Instituto de Radioproteção e Dosimetria/Comissão Nacional de Energia Nuclear (IRD/CNEN/MCT) and by the Chemistry Department of PUC-Rio. — (*May 24, 2002*) .

CLINICAL STUDIES – GENERIC MEDICINES

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Presented by HELIO B. COUTINHO

Clinical testing is not the only way to discover drug effects on people. That is the reason controlled clinical trials are the only legal basis for central regulatory agencies in each country, such as FDA, to conclude that a new drug has clinical effectiveness for a drug or biologic. Before clinical testing begins, researchers analyze the drug's main physical and chemical properties in the laboratory and study its pharmacological and toxic effects in laboratory animals. On the other hand, bioequivalence studies are the clinical test used, most often, when a sponsor proposes manufacture a generic version of an approved off-patent product. The law 9.787 (1999), established the legal basis for the institution of generic drugs in Brazil. Our research group started clinical trial and bioequivalence studies, with collaboration of the Public Pharmaceutical Laboratory of Pernambuco State (LAFEPE), the Brazilian official company to pioneer the development of medicines for AIDS and herperviruses treatment, between 1995 to 1998, even before the establishment of generic policy in Brazil. In 1997 and 1998, LAFEPE was ranked in 21st market position vs. all public and private pharmaceutical laboratories in Brazil. The Aids medicines at a low cost increased the production and sales, and were the main reason of such inedited result.

As a result of the studies developed, the following medicines were introduced to the Brazilian market by LAFEPE: stavudine and zidovudine (AZT) capsules, ganciclovir injectable, lamivudine + AZT, didanosine, lamivudine, and zalcitabine tablets. The result showed bioequivalence for lamivudine tablets (RT) as the 90% CI for both Cmax (99,7) and AUC0-12 (96,7) geom. mean ratios lie within the 80-125% interval. On AZT + DDI therapy the plasma HIV RNA levels decreased $> 0,5$ log after 30 days. The ganciclovir clinical study showed similar results in reference product by the control of retinitis in Aids patients infected with CMV. The stavudine and zalcitabine clinical study demonstrated no adverse effects reported and biochemical parameters remained unchanged and within the reference range. The pharmacokinetics parameters found for AZT + Lamivudine tablet were: AUC0-12 (8975 e 12.189ng.h/ml); Cmax (7.330 e 3.610 ng/ml) respectively, similar to the reference medicine. — (*May 24, 2002*) .

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BACTERIOLOGICAL LARVICIDES OF DIPTERAN DISEASE VECTORS

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The bacteria *Bacillus sphaericus* (*Bs*) and *B. thuringiensis* serovar. *israelensis* (*Bti*), display toxic action on mosquitoes and black flies, important vectors of man disease, acting as per os larvicides. These sporulating bacteria show a major advantage over synthetic insecticides: selectivity due to the specific mode of action. *Bs* is toxic against some species of Culicidae while *Bti* is also highly toxic against Simuliidae.

Both bacteria produce, during the sporulation, crystals, which contain protoxins. *Bti* crystals contain four polypeptides of 123-, 135-, 72- and 28-kDa, respectively called Cry4A, Cry4B, Cry11A and CytA. For *Bs*, crystals contain a toxin (Bin) made of two polypeptides of 42- and 51-kDa, called BinA and BinB, respectively. The mode of action of these proteins on larvae involves the ingestion of crystals and spores in suspension in water. Inside the midgut lumen, under the action of the alkaline pH and proteinases, protoxins in the crystals are solubilized and activated. Released toxins bind to apical microvilli of midgut cells, then cytopathological alterations are observed in midgut cells, leading to the death of larvae. Those toxins need to act in synergy to display the full toxicity and also bind to specific receptors in the larval midgut. Recently, the receptor of the Bin toxin of *Bs* in *C. pipiens* larvae was identified as being an α-glucosidase of 60 kDa.

Bti and *Bs* based larvicides have been produced and successfully used in vector control programs throughout the world. *Bti* has been mostly used to control species