Drug studies in developing countries*

Piero L. Olliaro,[1] Ramani Vijayan,[2] K. Inbasegaran,[3] Chim Choy Lang,[4] & Sornchai Looareesuwan[5]

One of the common features of "developing countries" in terms of pharmaceuticals is the lack of ability to generate independently the drugs that they need. These countries have to rely primarily upon products researched and developed by the pharmaceutical industry of richer countries — indeed, generics are often produced and used in the developing countries when proprietary compounds outrun their patent restrictions. This dependency has vast repercussions, but here we will focus only on the clinical end of the spectrum.

With few exceptions, drugs are researched and developed by the pharmaceutical industry of industrialized countries for the diseases prevalent in those countries, and their profiles are tailored to their own customers, including dosage, acceptability, and — not least — pricing. Therefore, the problem to be faced is the availability of the right drug, or even any drug at all, in developing countries. The western pharmaceutical industry has produced only a negligible number of so-called "orphan drugs" for tropical or "neglected" diseases (Trouiller P, Olliaro P. Drug development output: what proportion for tropical diseases? *Lancet*, 1999, 354 (9173): 164).

There are other ramifications as well. Several regulatory authorities in developing countries do not have a system to deal with new chemical entities, as only products that have been developed, reviewed and registered elsewhere are considered. Local regulations may require a clinical trial to be repeated in a developing country when a new compound is submitted for marketing authorization. Thus, clinical researchers often do only studies of secondary importance and limited scientific interest on drugs that have been already researched. We believe that such an approach is inadequate. Ethical aspects related to research in the tropical world should not be forgotten, though they have no easy solution.

Fortunately, there are some notable exceptions in the field of research into tropical and other diseases: China, India, Malaysia and Thailand, for instance, have been contributing pivotal studies of drugs for malaria and leishmaniasis with undeviating commitment.

In addition to providing meaningful information on drug efficacy and safety, a drug's pharmaceutical development project should also provide prescribing information so that the drug is used in an optimal manner. In this respect, it is becoming increasingly obvious that not all individuals respond uniformly to drugs and that ethnic variability necessitates better-adapted treatment recommendations (Wood AJ, Zhou HH. Ethnic differences in drug disposition and responsiveness. *Clinical Pharmacokinetics*, 1992, 70: 350–373; Lang CC et al. Attenuation of isoproteronol-mediated vasodilatation in blacks. *New England Journal of Medicine*, 1995, 333: 155–160). The use of a population approach to pharmacokinetics and pharmacodynamics is growing in modern pharmacology, in order to consider these differences between population subgroups and to provide information that will generate guidelines for individualizing dose regimens. Traditionally, the role of individual variables has been underestimated, and a drug's development programme that deals properly with dose adaptation based on, for example, ethnic differences in metabolism or mean body weight is very much needed.

We believe that developing countries do not need to conduct small clinical trials to duplicate information that already exists on drugs which are being considered for registration. It is questionable whether such work can contribute to knowledge or help to familiarize physicians with a new product, or whether it is undertaken simply to provide reassurance to the legislators as part of regulatory practice. Instead, these countries should contribute quality information which is relevant to the establishment of optimal treatment guidelines.

As a first step, countries should create and support national guidelines and centres of excellence. For example, the Ministry of Health of Malaysia has recently produced national good clinical practice (GCP) guidelines and is organizing courses to promote them at various levels. It has also established several centres of excellence to carry out clinical trials of drugs. These centres will then become potential sites for various types of clinical trials, including pre-registration (phase I, II and III) studies.

Similarly, emphasis has been placed on good laboratory practice (GLP). Malaysia enjoys one of the rare GLP analytical laboratories in the developing world. Some phase I and phase II studies in malaria have been conducted jointly between Malaysia and Thailand, building mutually upon the assets and

* All the authors participated in the Round Table on ''What sort of drug studies in developing countries?'' held in Kuala Lumpur, Malaysia, on 1–4 November 2000.

[1] Manager, Research on Drug Resistance and Policies Task Force, UNDP/World Bank/WHO Special Programme on Research and Training in Tropical Diseases, World Health Organization, 1211 Geneva 27, Switzerland; Chairman of the Round Table. Correspondence should be addressed to this author.

[2] Department of Anaesthesiology, University of Malaya, Kuala Lumpur, Malaysia.

[3] Department of Anaesthesia and Intensive Care, Kuala Lumpur Hospital, Malaysia.

[4] Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia.

[5] Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

Ref. No. **01-1269**

facilities of both countries. Concomitant HIV vaccine clinical trials are conducted in Thailand and the USA, and dengue vaccine clinical trials in Thailand and France. It is expected that, provided the ultimate product is affordable, these activities will benefit both the industrialized and the developing worlds, through the development of human resources.

Major multinational pharmaceutical companies should form partnerships with researchers in these centres of excellence to carry out both drug development and trials. These partnerships will benefit both the industry (by enhancing acceptability and approval by local regulatory authorities, increasing the rate of recruitment, and broadening the genetic diversity of the population exposed) and the researchers (who will be seen to be contributing significantly to new drug development).

Furthermore, recent emphasis on alternative designs (such as large, simplified trials, trials that focus on the complexity of population pharmacokinetics and dynamics, and pharmacovigilance) would increase the potential for countries to contribute significant data to adapted treatment regimens. Developing countries should be enabled to acquire the know-how and technology to participate more actively in the development of the products they need. ■