

## EDITORIAL

# Needed: closer scrutiny of clinical trials

C M GULHATI

Editor, *MIMS*, India. 90, Nehru Place, New Delhi 110019. e-mail: mims@ndb.vsnl.net.in

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How many people know that eight patients in Hyderabad who were administered recombinant streptokinase to test its efficacy and safety have died? According to the Genetic Engineering Approval Committee (GEAC), the trial was being conducted by the drug's manufacturer Shantha Biotechnics without taking clearance. Not surprisingly, the company denies the allegation claiming that it had taken permission from the Drugs Controller General, India (DCGI). In this game of passing the buck, no one is shedding any tears on the lives lost or compensating the families of those whose loved ones have died. Without any independent enquiry, the death of 'trial subjects', as they are impersonally called, has been attributed to 'causes other than the use' of the drug!

Not long ago Dharmesh Vasava, a 22-year-old healthy 'volunteer' from Bharuch in Gujarat, died while participating in tests on citalopram, an antipsychotic drug sponsored by Mumbai-based Sun Pharmaceuticals. According to another participant of the same trial, the subjects were lured with money by agents working for the company. Needless to say, such exploitative inducements are both unethical and illegal.

More recently, over 400 unsuspecting young women were used as guinea pigs by self-styled researchers to test if an anticancer drug Letrozole can help in ovulation. The trials were conducted illegally, without taking permission from the DCGI, predominantly at private clinics not recognised as research centres. At least one 'investigator' with just a diploma in gynaecology could hardly claim to be qualified or competent enough to try untested drugs. Strangely enough, based on documents submitted by the innovator of the drug Novartis, both the USFDA and the British Authority (MHRA) have labelled Letrozole as embryotoxic, foetotoxic and teratogenic at miniscule doses! The results of the apparently sponsored trials were extensively used by a Mumbai-based company to illegally promote Letrozole for induction of ovulation.

It may sound incredible but animals subjected to experiments in the United States enjoy more protection than humans in India. Any trial done on animals without the authority of the Ethics Committee is fined Rs 120,000 (US\$ 2,500) under the US Animal Welfare Act. In India, more than 400 young women have been treated worse than animals in America. Such unethical and illegal trials are conducted without any fear because regulatory authorities, either by design or default, fail to take action.

A couple of years ago, new chemical entities called M4N and G4N, discovered in the US, were unlawfully tested on 26 oral cancer patients at the Regional Cancer Centre (RCC) at Thiruvananthapuram. Under unrelenting pressure from the media and NGOs, an unwilling government was literally dragged into take action. Instead of penalising the guilty, further research on M4N and G4N was merely suspended for six months! In such cases, the law provides for three months' imprisonment for the guilty.

Legally, all clinical trials require DCGI permission and approval by the concerned hospitals' Ethics Committees. Research can only be conducted at recognised centres by duly qualified and experienced investigators. In practice, the DCGI approves clinical trials the same way as ration cards are issued by food inspectors. Some examples:

- As per the rules, trials of foreign drugs are permitted in India at one step below the phase completed abroad. Yet, the DCGI approved Phase III trial of Pfizer's Zoniporide even when

Phase II trials had not been completed in the USA. Furthermore, carcinogenic and reproductive studies on animals mandated by Indian law had not been completed.

- Cilansetron, a new molecule of Solvay Pharmaceuticals, not approved anywhere in the world, was cleared for Phase III trials even though only Phase II trials had been conducted abroad.
- Cilostazol, a product of Otsuka, was cleared by the DCGI based on incomplete, inadequate information on adverse effects. Common serious side-effects such as angina and myocardial infarction were not even mentioned. Needless to say, such omissions can be life-threatening for the study subjects.
- The protocol of the drug Tacrolimus submitted by Panacea Biotec and cleared by the DCGI was not only vague but also deficient and defective beyond imagination. It did not even state the phase of the trial, an elementary requirement, and omitted all important serious adverse effects such as malignancies, cardiomyopathy, lymphoproliferative disorders, etc.

It appears that some protocols and accompanying documents, such as Investigator's Brochures, are not even read by the DCGI. Otherwise, how does one explain the approval of patently defective clinical trials? This perception is strengthened by the super speed with which some proposals are cleared: a voluminous protocol on trastuzumab sponsored by Roche was approved within 5 working days. It is humanly not possible to read and analyse the bulky documents in such a short period.

Most of the clinical trials in India are conducted without any arrangement for compensation in case of study-related injury, disability or even death in human subjects. The ICMR Guidelines specifically require that each research 'shall include in-built mechanism for compensation for the human subjects...to cover all foreseeable and unforeseeable risks.' Despite this clear requirement, the DCGI routinely approves trials where no such undertaking is given by the sponsors.

The investigators for clinical trials, particularly when drugs are to be tested, are chosen by sponsoring companies. All manufacturers want that their products should be found safe and effective. There cannot be a better way to ensure positive results than to select friendly, obliging and ever-willing investigators to do the bidding. Many investigators who conduct clinical trials are, or have been, beneficiaries of largesse from the pharmaceutical manufacturers. The financial ties include paid speaking engagements, equity of the sponsoring companies, expensive gifts such as cars, refrigerators, air conditioners, medical equipment, attendance at sponsored scientific conferences, paid consultancy work, authoring 'ghostwritten' scientific articles, and travel grants for domestic and foreign travel. In 2002, a Mumbai-based company marketing erythropoietin had obliged some 300 senior nephrologists to visit Singapore on an expense-paid jamboree, an effective strategy not only to garner more prescriptions but also to ensure positive results of future clinical trials. Neither the regulatory authorities nor the ethics committees seek conflict of interest information from investigators.

Another important area concerns the right to publish the results of trials. For obvious reasons, no sponsor would like to publicise unfavourable results. With few exceptions, most protocols bind investigators to seek prior permission before publishing the trial results. This practice needs to be curbed. The rules on clinical trials should be amended to insert a clause to make 'Freedom to Publish' an essential criteria for approving trials. The world's top medical journal editors have already decided that trials which restrict investigators the freedom to publish will not be accepted.

It is often argued that India should not be left behind in what is grandiosely described as 'cutting-edge technology' of drug development. If at all India is to become a big player, it will have to actually discover or synthesise new drugs. Testing them in humans hardly involves any advanced technology. There are preset procedures that can be found in any good book on human trials. No wonder American companies have found doctors in Viet Nam as competent as those in India in this field. Unless laws are honestly implemented by regulatory authorities, the current unsupervised, unethical and often illegal clinical trials will pave the way for similar trials in gene therapy that will leave many Indians diseased, deformed and even dead. The way things are at present, the regulators officially designated as public servants are in imminent danger of becoming servants of the industry. WHO calls this phenomenon 'regulatory capture', i.e. the authority is seized by the very interests it is supposed to regulate.