

Standing committee report on CDSCO: hard facts confirm an open secret

Sandhya Srinivasan¹, Amar Jesani²

¹ Independent journalist, 8 Seadoll, 54 Chimbai Road, Bandra West, Mumbai 400 050 e-mail: sandhya_srinivasan@vsnl.com ² Trustee, Anusandhan Trust, Sai Ashray, Aaram Society Road, Vakola, Santacruz East, Mumbai 400 055 INDIA e-mail: amar.jesani@gmail.com

You would think the mandate of the Central Drugs Standard Control Organisation (CDSCO) is to ensure that medicines on the Indian market are safe, effective, and necessary for public health. But the government thinks differently. According to a statement by the ministry to the Department Related Standing Committee on Health and Family Welfare (1), the CDSCO's mission as stated in the committee's report, is to "meet the aspirations.... demands and requirements of the pharmaceutical industry". (1:8). It is no wonder, then, that this industry can do just about anything it wants, at the cost of people's health.

With the 59th report of this committee on the functioning of the CDSCO, for the first time, the internal workings of the office are laid bare for the public – with documentary proof of wrongdoing. The writers have minced no words in their indictment of the Drugs Controller General of India's (DCGI) office, their conclusions supported by a clearly articulated methodology and hard data. The report confirms what everyone knows: the regulatory body and a coterie of medical 'experts' are bounden to industry, and the approval process is a sham.

Dearth of resources to regulate

The report reveals a shockingly understaffed and abysmal infrastructure. Just 50 people handle applications for drug approval, and just 127 of 327 sanctioned posts are filled, though 1,045 are proposed. Just nine deputy and assistant drugs controllers handle 20,000 applications of various types, inspecting labs, 10,500 manufacturing units, and 600,000 sales outlets; providing information to parliament; meeting the public, attending court cases, and so on. And the CDSCO is headed by a drugs controller whose post demands nothing more than a graduate degree in pharmacy. The problem is compounded by a grossly inadequate infrastructure including data maintenance and coordination between state-level offices. The office is expected to review and decide upon an average of 1,600 applications for new drugs every year.

This state of affairs, well known to anyone who has interacted with the DCGI's office, is conducive to the larger scenario described by the committee: a nexus between regulator, industry and medical 'experts' which enables companies to sell, in India, dangerous drugs not approved in other countries.

New (foreign) drug approval – the CDSCO way

The committee carried out a systematic investigation of the approval of new foreign drugs, looking at two document trails. Its findings in both cases are shocking.

In one part of its investigation, the committee drew a random sample of 42 from the total 2,167 new foreign drugs (less than 2%) approved by the CDSCO from Jan 2001 to Nov 2010. Of these 42 drugs, all documents were missing for three (7.1%). Of these three, one was not approved in countries with strong regulatory bodies, and the other two had been withdrawn. The committee expresses doubts as to whether this "disappearance [of documents] was accidental" (1: 26).

Of the remaining 39 drugs on which information was made available, the mandatory Phase 3 trials on the drug's safety for the Indian population were waived in 11 (28.2%). 13 (33.3%) did not have permission for sale in any major developed countries. Not one of these 13 drugs has any special or specific relevance to medical needs in India. 25 drugs (64%) were approved without seeking any expert opinion; in the remaining 14 (36%) the opinions of only three or four experts was obtained. In two of 39 (5.1%) drugs, trials were on less than the minimum 100 patients, and in one (2.6%) on less than the minimum three centres. Four (10.3%) drugs were approved with neither clinical trial nor expert opinion. Finally, the CDSCO could provide Periodic Safety Update Reports (mandatory as part of post marketing surveillance) of only eight out of 39 drugs.

The committee also obtained information on all new foreign drugs approved without any clinical trial in India from January 2008 to October 2010 (34 months). The CDSCO gave a list of 31 such drugs, but the committee identified two more drugs that met these criteria. Thus 33 new foreign drugs were approved in 34 months -- almost one every month – without the required clinical trials here.

The committee demolished the CDSCO's and the health secretary's claims that these 33 approvals were given in the "public interest" – in response to an emergency such as a serious epidemic situation, for which presumably the law waives these requirements. None of the drugs approved was for such an emergency; some were pain killers, appetite stimulants, appetite suppressants, and anti-depressants. The CDSCO claimed that these drugs were approved after getting expert opinions and submission of the mandatory PMS data. However, expert opinions were collected in only five of 33 (15.2%) drugs -- and the CDSCO could not produce post marketing surveillance data on those drugs.

Other questionable practices of the CDSCO

The report highlights many other questionable practices of the CDSCO. It records specific examples of unlawful approvals (such as Buclizine, Letrozole, Deanxit and a placental extract). It gives examples of state FDAs acting on their own, and manufacturers

deliberately using confusing brand names. It notes that there is no mechanism for withdrawing drugs found to be substandard. About drug information, it states that the CDSCO doesn't ask companies for updates, so companies don't provide them. Finally, drugs are advertised directly to the public in violation of the law, but do not provide consumers basic information on these drugs as is required abroad.

Collusion between industry, regulator and expert

The committee is scathing in its comments on the manner in which regulators and doctors, who are expected to use their expertise and power to ensure safe, effective and necessary drugs, collude with industry.

The report names several senior clinicians who have provided expert opinions that companies have used to introduce their drugs without clinical trials, and has annexed copies of their opinions. "A review of the opinions submitted by the experts on various drugs shows that an overwhelming majority are recommendations based on personal perception without giving any hard scientific evidence or data... Still worse, there is adequate documentary evidence to come to the conclusion that many opinions were actually written by the invisible hands of drug manufacturers and experts merely obliged by putting their signatures." (1: 33) It concludes that "many actions by experts... are clearly unethical and may be in violation of the Code of Ethics of the Medical Council of India applicable to doctors. Hence the matter should be referred to MCI for necessary follow up and action. In addition, in the case of government employed doctors, the matter must also be taken up with medical colleges/hospital authorities for suitable action." (1:36)

Second, many experts appointed on the CDSCO's advisory committees are from Delhi and surrounding areas, so much so that one expert from Delhi "sat on 5 of the 6 committees (1: 46).

Committee recommendations

The committee's recommendations include punishment of those found guilty of the various violations it lists -- the companies marketing drugs that are banned in other countries, the doctors who signed 'expert opinions' for such drugs, and the officials who gave a rubber stamp of approval to the sham. The committee also calls for transparency in the approval process: guidelines on selection of experts, declaration of conflicts of interest, and experts' opinions to be made public.

The committee notes that the current requirement of phase 3 trials on 100 patients, to look at the drug's impact on the ethnic groups in India, is unscientific and therefore unethical. It is also viewed by industry as a technicality, a matter of generating paperwork -- though even this is bypassed when possible, as the report reveals. The committee recommends that 'phase 3 trials' in India for approval here have larger, representative samples to detect any differences in the drug's metabolism in various ethnic groups, and with more rigorous monitoring.

However, the notion that ethnic diversity is represented through outward physical characteristics is scientifically questionable. Nutritionists have suggested that differences in how drugs are

metabolised by malnourished people is more relevant; however this cannot be tested ethically. The focus should be on whether the drug is essential, or irrational, or just another me-too drug, and on an effective system of pharmacovigilance for all side-effects, adverse events and deaths.

Likewise, in the absence of any functioning system of pharmacovigilance, the committee recommends that periodic safety update reports be substituted with controlled post-marketing trials. However, the absence of pharmacovigilance is a serious lacuna that cannot be filled with post-marketing trials.

Larger context of drug approval

Interestingly, in contrast to its clear-eyed analysis of the Indian scene, the committee holds the standards and functioning of regulatory bodies such as the USFDA in high esteem. Contrary to the committee's judgment, though the USFDA's mission statement is "protecting the public health", the FDA is not very different from the CDSCO in its functioning, fraught with irregular decisions because of industry funding. With the Prescription Drug User Fee Act (PDUFA), 1992, industry provides the FDA's Centre for Drug Evaluation and Research money to pay for staff and infrastructure and provide time-bound review of applications. As a result, the FDA commissioner recently argued, justifying industry-funded regulation: "We lead the world in the number and speed of drug approvals... To achieve these results, and speed access for the American people, we made use of accelerated approvals and flexible clinical trial requirements and made sure manufacturers know that marketing applications can be based solely on foreign clinical data that meets certain clear and specific requirements." (2)

With the renewal of the PDUFA in May 2012, industry will provide almost half of the agency's budget of \$4.5 billion (3) In fact, 98% of the FDA's budget increase will be covered by the increase in user fees (2). Further, the FDA permits consultants for drug companies to serve on its own 'expert committees'. Waivers are granted to conflict of interest guidelines. It is no surprise when these expert committees vote to keep on the market drugs that have harmed people, even killed them, even when safer alternatives are available (4). Clearly the money and guidelines have not kept dangerous drugs off the American market.

There are ethical implications in a regulatory body taking money from the very industry it is supposed to regulate. The regulator should be sufficiently funded through taxes on the drug industry and contract research organisations (CROs).

The USFDA's industry-driven requirements have also fuelled growth, in India, of outsourced drug trials with no scientific value and with evidence of unethical and dangerous practices. Its insistence on placebo-controlled trials of drugs even when an effective treatment exists comes from industry's need to show the effect of me-too drugs of marginal value, even if they are less effective than the current treatment. One reason the FDA accepts data from outsourced trials is that such trials cost industry less. Another is that placebo-controlled

trials may not be permitted in the US. For the same reason, it waived international ethical guidelines when they became inconvenient to such requirements.

The US FDA is brought into this discussion because its consequences are felt in India, when industry lays down the agenda for drug approval and research, such as in encouraging outsourced drug trials in India. The DCGI accepts data submitted to the FDA towards marketing approval here. India does not need to emulate the US FDA. Any suggestion that money to meet staff and infrastructure shortages come from industry should be opposed vigorously.

Government response

Many of the committee's recommendations along with the report's findings could result in a regulatory body that is accountable to the people whose health and lives it is supposed to protect. Given the extent of wrongdoing documented by the committee, the findings justify action not only on the 39 cases it investigated; approval documents for all drugs at least from 2001 to the present must be investigated. Indeed, transparency at all levels of the approval process is a critical step in making the organisation accountable to the public. The same is true of the proceedings of ethics review committees which function as regulators in drug trials.

However, the government's response – to appoint yet another committee to further investigate the findings – do not give confidence that the report will have an impact on

the regulation of the drug industry in India. The committee members come from the same coterie of experts referred to in the Standing Committee report. The Indian Council of Medical Research, whose director is a committee member, was part of the HPV vaccine trial that is now established to be grossly unethical. Another member headed the committee that investigated the HPV vaccine trial and identified the various unethical practices but concluded that no one person could be held responsible for them.

Any further investigation should come from non-interested parties, and the findings and action taken must be made public if this report is to have any value.

References

1. Department-related Standing Committee on Health and Family Welfare. Fifty-ninth report on the functioning of the Central Drugs Standard Control Organisation (CDSCO). New Delhi; Rajya Sabha Secretariat; 2012 May.
2. Hamburg MA. President's fiscal year 2013 budget request for the FDA. US FDA [Internet]. 2012 Feb 29. [Cited 2012 May 27]. Available from: <http://www.fda.gov/NewsEvents/Testimony/ucm293842.htm>
3. Yukhananov A. US Senate passes bipartisan FDA funding bill. Reuters [Internet]. 2012 May 24 [cited 2012 May 27]. Available from: <http://www.reuters.com/article/2012/05/24/congress-fda-idUSL1E8GOGS020120524>.
4. Angell M. FDA: this agency can be dangerous. The New York Review of Books. 2010 Sep 30; 66-8. http://www.ahrp.org/cms/images/stories/articles/angell_fda_dangerous.pdf

Technology in health care: current controversies

Editors: Sandhya Srinivasan, George Thomas

Published by: Forum for Medical Ethics Society and Centre for Studies in Ethics and Rights, Mumbai. December 2007. 288 pages. Rs 200

This collection of essays covers important discussions related to medical technology that have been carried in the *Indian Journal of Medical Ethics*. Each of the nine sections is preceded by a commentary by an expert in the field. The nine chapters cover placebo controls in research; intellectual property rights; family planning and population control; the HIV/AIDS programme and research; electro convulsive therapy without anaesthesia, liver transplant technologies, end-of-life care, medical professionals and law enforcement, and technology in public health programmes.

To order copies, please send a demand draft or cheque in favour of "Forum for Medical Ethics Society" to Forum for Medical Ethics Society, c/o Survey No. 2804-5, Aaram Society Road, Vakola, Santacruz(E), Mumbai 400 055 INDIA e-mail: ijmemumbai@gmail.com