A Stinging Indictment of India's Drug Regulation Authority

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The Central Drugs Standard Control Organisation is expected to protect the citizen from the marketing of harmful pharmaceuticals. The findings of the 59th report of the Parliamentary Standing Committee on Health and Family Welfare are an expose of the shockingly lax standards followed by this so-called standards organisation, the casual approach taken in certifying drugs for sale, and the unethical and illegal steps taken by some pharmaceutical companies and medical practitioners in pushing for the introduction of certain drugs in the market. Can and will the government act?

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The 59th Report of the Department-Related Parliamentary Standing Committee on Health and Family Welfare[1] is a stinging indictment of the state of affairs in the Central Drugs Standard Control Organisation (CDSCO).[2] The report deals with problems specific to regulation of modern medicine[3] and is probably the tip of the iceberg.[4]

We summarise some key points made in the report.

Structural Issues in CDSCO

The status report of the CDSCO says its mission is to "meet the aspirations… demands and requirements of the pharmaceutical industry". The CDSCO seems to have got all its priorities wrong: "For decades together it has been according primacy to the propagation and facilitation of the pharma industry, due to which, unfortunately, the interest of the biggest stakeholder, i e, the consumer has never been ensured" (Para 2.2 of the report).

In contrast, the stated missions of drug regulatory authorities of developed countries explicitly talk of protecting/safeguarding public health by assuring the safety, efficacy, and security of humans involved. Disservice to the consumer and neglect of public health goals have a boomerang effect in the long term. Complicit in this are India's pharmaceutical companies with their penchant for making unessential, harmful medicines and irrational Fixed Dose Combinations (FDCs). Also complicit in this is the medical profession. Why have the leading elites of the medical profession been quiet – especially those in positions of power? The patient has no choice in the matter.

The report comes down heavily on "equating" B Pharms with MDs in pharmacology and/or microbiology. And says that the latter, and the pool they come from, should be given preference for appointment to the job of the Drugs Controller General of India (DCGI). Well, Hobson's choice really. One of the best commissioners of the Food and Drug Authority (FDA) in Maharashtra was an IAS officer, Arun Bhatia, but shunted out soon because of his effectiveness. At the helm, we need persons of vision with an understanding of the importance of evidence-based medicine in public health and curative healthcare, as well as an understanding of the general progress of science of medicine, pharmacology and pharmaceutics – these may be found in a wide range of associated disciplines. An understanding of the political economy of the pharma industry certainly would help. What will not help is a tendency to go along with pharma industry propaganda or medical fashions. There is also a case for making the CDSCO an independent drug authority like the Indian Space Research Organisation and the like, with the DCGI being given Government of India secretary level status.

Regulatory Anarchy

The part of the report (Para 7 onwards) on issues related to drug approvals and withdrawal of medicines, banned and ought to be banned, should give sleepless nights to the CDSCO and the Ministry of Health.

The CDSCO had approved 2,167 medicines from January 2001 to 30 November 2010. Files of three medicines – from a randomly chosen list of 42 medicines out of the 2,000 plus recently approved medicines – were not traceable. These medicines – pefloxacin, lomefloxacin and sparfloxacin – also happen to be controversial. All three medicines are sold in India but not sold in any of the countries with well-developed regulatory bodies. Of the remaining 39 drugs, the committee found the following problems: In the case of 11 medicines, Phase 3 trials were not conducted. In the case of four approved medicines, neither Phase 3 trials were conducted nor expert opinion sought. In some cases, drug trials were not conducted on the legally required minimum of 100 patients. Or were conducted

only at two hospitals as against at three to four sites, the legal requirement. Out of the sample of 39 approved medicines, 13 (33%) of the medicines were not permitted for sale in the US, Canada, Britain, EU and Australia. These 13 medicines, that included 10 irrational FDCs, are not relevant to India's medical needs. In the case of 25 medicines (64%), expert medical opinion was not sought before approval. In those cases (14 out of 39) where medical opinion was sought it was restricted to three to four experts. Medical opinion that is given, either for or against, is not easily accessible let alone in the public domain on a website. The general public has a right to know who said what.

Between January 2008 and October 2010, 33 medicines were approved without any clinical trial. One thus does not know anything about their safety and efficacy. Granted that the Drugs and Cosmetics Act 1945 and especially Schedule Y of the rules (especially 122A, 122B, 122D, 122DA, 122DAA and 122E) contain several clinical trial waiver clauses. But they are to be waived in the case of emergency (say swine flu and H1N1 vaccine) or in public interest. None of these 33 medicines fell under these categories of emergency or public interest.

The DCGI also cleared trial sites for Phase 3 without application of mind as to whether they represent the needed ethnic diversity. The committee recommends an increase in number of persons accordingly to take into account ethnic diversity. We comment on this later.

Medical opinions sought from experts appeared to have become a farcical exercise. Opinions were given in a subjective fashion without citation of any hard scientific evidence. Also the letters of many of the experts read almost verbatim (Para 7.31), which leads one to suspect that the whole process was considered a mere formality with the expert appending his/her signature on the draft supplied by the pharma company, the saving grace being the letterheads were their own! In the case of an FDC of acelofenac and drotaverine, not permitted in any country in North America, a CDSCO official advised the manufacturer Themis Medicare, to select experts, get the approval letters written and send them to the DCGI. Of course they were all in identical language. The official and the company, and the experts, in this case as in others, need to be taken to task for the unholy nexus. Doctors complicit in the charade of giving "opinions" may be deprived of their degrees or right to practice for a given period for violating their codes of ethics.

Experts chosen were conveniently based in Delhi, in a vast country with 7,00,000 doctors, without checking whether their experience was relevant to the particular class of drugs ("One wonders whether expertise on medicines is confined to Delhi", Para 8.10). And of course there was no checking out whether there were any conflicts of interest. Specifically the committee took the CDSCO to task for illegal approval of four drugs: Buclizine approved without clinical trials and consideration of its effects on children; letrozole (a breast cancer medicine approved also for infertility in women without any Phase 2 studies – since banned by the DCGI for use in fertility); FDC of flupenthixol and melitracen (Deanxit), a medicine prohibited for sale and use in Denmark in the country of its origin and approved in India in violation of Rule 30B of the Drugs and Cosmetics Act; and illegal approval of new indications of placental extract gel (new indications and new formulation mean it is a new drug as per Rule 122E(b) but the same was not treated as a new drug – clinical trials were therefore not requisitioned). The ministry/CDSCO is expected to give a reply by 8 July on action taken on erring officials, retired since or serving, who were responsible for approval of these four drugs. A move that is likely to deter mindless approvals for some time at least.

Other Recommendations

The committee goes on to make other important observations and recommendations:

(1) Remove unauthorised FDCs (those approved by state authorities, without clinical trials and without prior clearance from the CDSCO, in spite of being new drugs as per Rule 122E(c)). The powers in the Drugs and Cosmetics Act under Section 33P and Section 26A are sufficient to remove all such FDCs, especially ones having combination of antibacterials that have the possibility of increasing drug resistance (Para 9.8).

(2) Transparent criteria for selection of persons for Drug Advisory Committees and from all over the country (Para 10.2).

(3) Remove confusion over near sounding and similar brand names. A database of all brand name medicines with their ingredients should be made available on the CDSCO website (Para 11.2).

(4) Insist on pharma companies to send India-specific Periodic Safety Update Reports (PSURs) as part of post-marketing surveillance. PSURs were available for only eight of the 42 medicines randomly selected (Paras 12.2 to 12.6).

(5) Phase 4 studies to be conducted for detecting adverse effects in lieu of the ineffectiveness of pharmaco-vigilance programmes (existing and planned) (Para 13.3).

(6) Constant updating of information on medicines already marketed. Manufacturers have obligations as per law to provide such information and they need to be penalised as per rules for non-updating of information (Para 14.3).

(7) Stringent punishment for those responsible for spurious and substandard drugs. And penal provisions also for manufacturing misbranded and adulterated drugs may be considered (Para 15.6).

(8) Appropriate action on companies that have advertised Schedule H medicines in lay press. Sharper teeth to the Drugs and Magic Remedies (Para 16.2).

(9) Consumer information on medicines in all major languages "at the click of a mouse".

(10) Issues related to clinical trials of medicines would be taken up for separate detailed examination by the committee (Para 18.2).

The Road Ahead

On Quality: The report makes several recommendations regarding shortage of staff, laboratory facilities in the states, etc. We believe these are being addressed in the Twelfth Five-Year Plan and so we will await implementation.

The burgeoning pharma sector generates its own pressures on medicine

regulation. No amount of increase in resources and laboratories is going to ensure quality because the supply of laboratories and facilities would not be able to keep up with the demand for regulatory oversight. Therefore the achievement of quality must be enabled in other ways also. We would suggest that the parameters of good quality, good manufacturing practices and good clinical and storage practices are spelt out in a transparent way that can be interpreted and implemented without ambiguity. Second, manufacturers found wilfully making substandard, misbranded and/or spurious drugs must be tried in special drug courts to expedite matters in a competent manner. There is a demand for capital punishment in some quarters, a kind of overreach this writer does not agree to. There is now a provision for life imprisonment. That is a sufficient deterrent. These powers need to be used in a fair and fearless manner; and any rent collection by drug authorities or quid pro quo with manufacturers should invite summary administrative action from suspension to dismissal.

Action on the bribe giver and taker is necessary, as also rewards for whistleblowers from within the CDSCO and not only for the general public. Also consumers and prescribers need to be educated on what constitutes quality in a medicine. Special medicine quality testing kits need to be made widely available.

We may also observe in passing that quality standards have gone up especially of those manufacturers exporting to countries with well-functioning regulatory agencies. It is in the manufacturer's self-interest. Hence wide publicity to substandard medicines (apart from the odd batch failing in spite of best efforts) should discourage wilful mischief makers.

Rationalising the Workload: The CDSCO is groaning with excess workload. Many of the problems of work overload of the CDSCO and the State Drug Commissionerates are self-inflicted. We have too many medicines and far too many of them do not find mention in standard textbooks of pharmacology. The first act of cleaning the stables would be to remove all those medicines that are unnecessary, irrational and of doubtful value. These would include swift weeding out of harmful medicines like analgin. Allow only standard dosages and formulations of the remaining which would be about 800-1,000 molecules. Weed out unauthorised FDCs using powers given to the CDSCO under Section 33P and Section 26A. There still would be authorised FDCs but these would include irrational medicines. A committee may be appointed to weed out these on broad principles of when FDCs can be deemed rational and what kind of FDCs would be irrational and must therefore be weeded out. These measures would apply to vaccines also. In addition, the principle enunciated in Para 9.8 of the report must be used: "In general, if an FDC is not approved anywhere in the world, it may not be cleared for use in India unless there is a specific disease or disorder prevalent in India, or a very specific reason backed by scientific evidence and irrefutable data applicable specifically to India that justifies the approval of a particular FDC." This must be applied to any medicine.

Also strict use of Rule 30B of the Drugs and Cosmetics Act prohibiting import of drugs banned in the country of its origin would minimise entry of unwanted and useless medicines in the country. We feel implementation of these measures would considerably increase efficiency in decision-making in the CDSCO. At the risk of an inappropriate analogy, it is like increasing the power availability in the country by cutting down transmission losses.

Debranding: We agree with the recommendation on near sounding brand names. But why not remove brand names completely, "debrand" as the Pronab Sen Task Force (2005) has recommended? India is the only country with significant manufacturing ability where medicines out of patent are sold under brand names.

Drug Approvals and Ethnic Diversity: Some of the measures recommended in the report would lead to an increase in the clinical trial load in the country. We would however urge that before these are implemented in toto, we need to have laws in place to regulate clinical trial misdemeanours, laws to regulate Contract Research Organisations, and laws for compensation on clinical trial injury. Whether increased requirements of clinical trials will end up increasing the tribulations of an already vulnerable population – the poor, tribals, etc – need to be given thought. The report has recommended taking into account ethnic diversity of the Indian population in Phase 3 clinical trial participants. Whether ethnic diversity within India is a significant factor in the pharmacodynamics and pharmacokinetics of every drug, the jury is still out.[5] There is no CDSCO guideline on the topic and it is not clear if any thinking has been done by India's research community on this issue. But this certainly is an area that needs thought. But an equally important consideration is to focus on pharmacology and drug effectiveness of undernourished populations.[6] What is the use if much of the medicine is excreted by undernourished populations? We certainly know that dosages are decided on the basis of western body weights.

Transparency, Conflict of Interests: Drug regulation in India is notoriously non-transparent: Non-transparency in the process of approval of new medicine formulations for manufacture and marketing,

lack of easy public access to research data used in approval of new medicines, and data related to all clinical trials. We also need a clear declaration of conflict of interest at all decision-making levels followed by recusal of those having conflict of interests. Both situations urgently need to be remedied.

A Law to Check Unethical Medicine Promotion and Updating of Existing Laws: Unethical medicine promotion is another way in which irrational use increases and impoverishes patients. The CDSCO has never taken curbing unethical medicine promotion as part of its mandate – partly because there is no clear law on the matter. This hiatus needs to be remedied quickly. Some civil society groups have already worked on such a draft law.[7]

There is a need for harmonisation of the provisions in sections of the Drugs and Magic Remedies (Objectionable Advertisements) Act, 1954, and Rules (1955), provisions of the Drugs and Cosmetics Act (Sections 17 and 18 on misbranded, adulterated and spurious drugs), Schedule J of the Rules to the Drugs and Cosmetics Act ("Diseases and ailments by whatever name described which a drug may not purport to prevent or cure or make claims to prevent or cure"). These all need to be harmonised and taken into account recent medical developments such that it will deter misleading advertisements as well as drugs and devices making fancy claims across the spectrum of systems of medicines. The laws are toothless in preventing fairness creams, presumably because this is not a specified condition in the Schedule to the Drugs and Magic Remedies (Objectionable Advertisements) Act and are neither in the list of items in Schedule J of the Rules to the Drugs and Cosmetics Act nor are claimed in the labels or cartons for action under the provisions of the Drugs and Cosmetics Act (Sections 17 and 18 on misbranded, adulterated and spurious drugs). Nevertheless, the drug commissioners have not made sufficient use of such powers that do exist (for instance, medicines for baldness, a specified proscribed condition in the said provisions, are routinely advertised with impunity). Or even in as simple a matter as advertisements in the lay press of Schedule H prescription drugs.

Consulting the DTAB for Banning Medicines: A matter requiring formal clarity is whether the Drug Technical Advisory Board (DTAB) needs to be consulted in the banning of drugs. The Report, Para 8.9, asks

> … at the time of approval of drugs, the matter is not referred to DTAB, then why should DTAB be involved when drugs are to be banned? Secondly, many drugs have been approved by DCGI without consultations with experts; why involve them when banning?

However it goes on to say that consultation as such is welcome. A recent judgment of the Madras High Court, even as we write this, has opined that the central government need not consult the DTAB in the banning of drugs.[8]

The government's response to the Parliamentary Committee Report has been to set up another committee. Hopefully this committee will not be an instrument to sweep matters under the carpet. If anything the 59th Parliamentary Committee Report is an opportunity to radically clean the anarchy in drug regulation in India in the interests of public health. Surely, "The Pharmacy of the World" deserves a better regulatory body.

NOTES

1 Rajya Sabha Secretariat (May 2012): Department-Related Parliamentary Standing Committee on Health and Family Welfare. Fifty-Ninth Report on the Functioning of the CDSCO, New Delhi (May 2012). Hereafter the report.

2 The CDSCO, headed by the Drugs Controller General of India, is the ultimate executive authority that licenses drugs for manufacture and marketing in India. It is the chief implementer of the following laws, among others, in the country: The Drugs and Cosmetics Act, 1940 and Drugs and Cosmetics Rules 1945; and the Drugs and Magic Remedies (Objectionable Advertisement) Act, 1954.

3 Drug regulation covers many functions including marketing approval of new medicines based on safety and efficacy studies; licensing and monitoring of manufacturing facilities and distribution channels; post-marketing adverse drug reaction (ADR) monitoring; quality control (QC); periodic review and re-evaluation of approved drugs; control of drug promotion; Regulation of drug trials.

4 The issues in regulation of drugs in other systems of medicine are likely to be at least as complicated, and as messy.

5 See S U Yasuda, Zhang L and Huang S-M (September 2008): "The Role of Ethnicity in Variability in Response to Drugs: Focus on Clinical Pharmacology Studies", *Clinical Pharmacology & Therapeutics,* 84 (417-23). See also US FDA Guidance for Industry: "Collection of Race and Ethnicity Data in Clinical Trials", September 2005, viewed on 5 June 2012 (http://www.fda.gov/RegulatoryInformation/Guidances/ucm126340.htm). "Ethnic Factors in the Acceptability of Foreign Clinical Data", September 2006, viewed on 5 June 2012. (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129323.pdf). The suggested race and ethnicity categories are at a minimum: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White. From Iraq to India to Japan, the differences are clubbed under Asian, a fact that may be amusing to Indian researchers.

6 I owe this reminder to Veena Shatrugna and C Sathyamala.

7 Outcome of a workshop organised by Consumer Action Group (CAG), Chennai, January 2011. The draft law can be added to the Rules section of the Drugs and Cosmetics Act.

8 "Centre need not consult DTAB before banning drugs, says High Court", *The Hindu,* Chennai, 3 June 2012 (http://www.thehindu.com/todays-paper/tp-national/article3485400.ece). "…. Rejecting the argument of a group of pharmaceutical companies that such consultation was mandatory, Justice V Ramasubramanian said that the court could not be forced to introduce a clause which had been deliberately omitted by the legislature. He pointed out that only other provisions of the Act, except for Section 26A, had made consultation with the DTAB obligatory."