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Indian drug approval mechanism under fire

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Drugs are launched in India without approval

On May 8, when Mr Brajesh Pathak, chairman of India's parliamentary standing committee on health and family welfare, presented its report on the way Central Drugs Standards Control Organization (CDSCO) works, it was akin to opening a can of worms. Although not a major surprise to those in the industry, it did come as a shock to the citizens of the country that at least 33 drugs currently in the market had never been tested on the Indian population.

The 118-page report speaks about the CDSCO, including its motto, the bending of rules for granting approvals to drugs, ignoring of the nexus between doctors and pharma companies and the problems faced by the less than stable office of the

drug controller general of India (DCGI). The authors of the report not only explored the inadequacies in the functioning of the CDSCO, but also investigated the malpractices.

The gaps in CDSCO's functioning

There exists many loopholes and several concerns associated with the drug approval system in India The statutory rules state that "an applicant for new drugs discovered outside India should conduct phase III trials on no less than 100 patients at three-four different hospitals in India to test the efficacy and safety of new drugs for proposed indication". Also, in such cases, the opinion of experts is sought to assess the need and fast track its availability to the Indian population. The post marketing surveillance of such drugs is mandatory. However, there are provisions where in public interest this rule can be waived off. This provision has been provided to allow for faster introduction of necessary vaccines in case of epidemics or life-saving drugs. But analysis has shown that this provision has been grossly misused.

As a part of the report, the standing committee randomly chose 42 drugs to study, which was a sample size of less than two percent of all drugs approved by the DCGI between January 2001 and November 2010. The office of the DCGI could not produce any documents on three of these 42 drugs. Of the remaining 39 drugs, it was found that 11 drugs were given approvals without carrying out the necessary trials. Pharma majors indicted on this account include MNCs such as Novartis, Eli Lilly and GSK and Indian companies like Cipla. Additionally, the committee points out that between January 2008 and October 2010, 33 drugs, which do not fall into the category of emergency medicines, have been approved without conducting the necessary clinical trials.

The main aim behind carrying out a phase III clinical trial for a drug discovered outside India is to test its safety on the Indian population, which is more diverse in terms of genetics than the Caucasian population or any other race on which the drug may have been previously tested. There have been a variety of explanations that have been offered by the DCGI for these trials not being necessitated. (Read more: Some of the comments made by the CDSCO were particularly blatant). The fact that trials were carried out beforehand in other countries which had people of different ethnicities "that could have include Indians"(as stated by the DCGI reply), was one of them though there was no evidence to back this claim.

In case of three other drugs where clinical trials were carried out, they were not in line with the required 100 patients on three-to-four trial sites. For this, the CDCSO said the trials were carried out in cosmopolitan cities, and hence presented sufficient diversity among the said patient population. A closer look at the location of the trials, however, revealed that they had been carried out in cities like Kota, Aurangabad, Bhopal and Vadodara that cannot exactly be defined as cosmopolitan. In some cases, these trials were carried out entirely by private practitioners. All these factors begged to raise the question if the trials were being carried out just for the sake of documentation.

Additionally, 13 drugs that were approved by the CDCSO were such that they are currently not approved for sale in any major developed countries, such as Canada, the US, Australia and the European Union. Even more surprising were examples of drugs such as Buclizine approved in 2006 for appetite stimulation in children without clinical trial or expert opinion. The drug developed in Belgium is not approved for the condition, appetite stimulation, even in its innovator country. The standing committee has sought a review of this approval.

In the case of four other drugs, neither the opinion of any expert was sought nor any clinical trials were conducted, but the decision for approving the drugs, as the report puts it, was "by the non-medical staff of CDSCO on their own".

The slew of reputed MNC pharma companies indicted in the report have raised pertinent questions on the approval system. In response to the allegation that their drug Ambrisentan was approved without mandatory trials, the spokesperson said the "drug was approved in Europe in 2008 and in the US in 2007 after evaluating 400 patients in two pivotal phase III studies. This complete global clinical data set was submitted by GSK to regulatory authorities in India in 2009 and since PAH (pulmonary arterial hypertension) is a rare disease which is life threatening and debilitating, GSK was granted a local clinical trial waiver in India".

Others such as Cipla have previously stated that "they have followed all the necessary regulations for the approval of their drugs".

Additionally, critics and supporters alike have called for a revision of the 100 patients rule. Whether it is sufficient for a nation of 1.2 billion or whether this size of patient pool is necessary for a drug that has already been thoroughly tested in clinical trials, albeit in a different country, needs to be addressed.

The curious case of invisible hands

Among other things, the report brought to light the nexus between doctors and pharma companies. It highlighted cases and presented definitive evidence of clear involvement of a third party in the process.

In case of the drug Clevudine (Phamasset), three experts, located at different corners of the country, sent in identical, word by word, letters of recommendation advising the approval of the drug. The third party presence becomes even more obvious in the case of Ademetionine (Akums) where all the four letters of recommendation carried the same mistake of addressing the letters to Directorate General of Health Services instead of DCGI. One of the opinions was also obtained within a day, raising questions on how the study of the drug was carried out in such a short time. The standing committee thus expressed if indeed there was a pair of "invisible hands" that were writing the letters of recommendation for drug approvals.

In another case for Pirfenidone (Cipla), four letters of recommendation from different parts of the country were obtained on the same day and were documented in a consecutive fashion as well, raising suspicions about another agency that collected all these reports and deposited them at the DCGI.

The report not only highlights the inadequacies present in the current Indian system, but also shows how similar drug regulatory bodies of other countries handle similar procedures. It shows how in the case of the USFDA, the comparatively large pool of experts - twenty medical practitioners - showed independent ways of thought and differed in final assessment. A remarkable fact was that these decisions and opinions were in the public domain on their website. Mr Prashant Reddy, blogger at SpicIP, one of the most authoritative blogs on IP protection, said, "The existing framework of drug regulation is more than 60 years old and so far its provisions have been amended mainly for the industry. The hitherto lack of information about CDSCO functioning has always been an issue. Transparency in a regulatory environment is necessary, especially when it comes to health matters."

In India, the expert opinions have also been placed far from public scrutiny unlike other countries as highlighted in report. Negative they might be, but the committee felt that the expert opinions deserve to be in the public domain as they have a paramount effect on the safety of the public.