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Is the Pandemic the Wake-up Call We Need on the Drug Regulatory Process?

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Sometimes it is the power of lobbies rather than Science that is now driving approval of new drugs, as seen in the questionable clearance to a few Covid-19 drugs; people end up willing to pay anything for these drugs though it is not certain that they work.

The second wave of the Covid-19 pandemic has revealed a deep rot in India's healthcare system. Our attention today is focused on the most visible failures; the pathetic state of public healthcare facilities in almost every state, and the acute shortage of doctors and nurses especially in the public sector. Somewhere in between this never-ending stream of depressing news, the *Times of India* reported that Glenmark Pharmaceuticals earned a record revenue of Rs. 352 crore in just the month of April and a total sum of Rs. 762 crore since June 2020 from the sale of Favipiravir, which was being prescribed to treat Covid-19.

The drug is sold under brand name Fabiflu, a name that is now familiar to all of us thanks to the repeated pleas on the social media by desperate relatives of Covid patients. When politicians began hoarding the drug only to hand it out sparingly to their supposed constituents, a formal complaint was registered against them. Among the heart-wrenching scenes that played out on television as people began to fall sick from the virus were the long lines of family members of the sick looking for the antiviral drug Favipiravir. Demand spiked, and that led to black-marketing and panic buying of the drug.

These record sales figures are intriguing since Favipiravir never made it into the Clinical Guidance for Management of Adult Covid-19 patients formulated by the AIIMS/ICMR-Covid-19 National Task Force. The reason for the drug's exclusion from the national guidelines is not public but the most likely reason is the fact that the clinical trial for this drug, which was originally developed by a Japanese company to treat influenza had failed to meet its primary end-point. Although the secondary endpoint was met, it was statistically insignificant and the entire clinical trial came under fire from the scientific community last year for its poor design. Some of us had publicly criticized the approval of the drug by the Drug Controller General of India (DCGI) on the basis of a recommendation from a Subject Expert Committee (SEC) whose membership at the time was not public. While the DCGI paid little heed to our warning, somebody at the National Task Force clearly agreed with our scepticism of the drug for this purpose and declined to list the drug in the national treatment guidelines. Yet this single drug earned its manufacturer a sum of Rs. 972 crore in less than a year. Such is the power of the marketing machine of the Indian pharmaceutical industry.

> It is as if no one in the Ministry of Health and Family Welfare or the Prime Minister's Office wants to look at this mess or have implicitly given their permission to the Central Drugs Standards Control Organisation to continue its charade.

While we mostly tend to discuss regulatory reform in the context of safety of our drug supply, the case of Favipiravir is a great example of how poor regulatory decisions, combined with the irrational tendency of Indian doctors to prescribe medication not supported by clinical evidence can lead to a transfer of a huge amount of wealth from ordinary citizens to the pharmaceutical industry. This is not to say that the DCGI has done a good job of ensuring safety and efficacy of the drugs and vaccines being provided to the Indian population. So far, the national regulator has maintained a pin-drop silence on the very serious safety concerns raised by the Brazilian regulator with regard to Bharat Biotech's Covaxin and the Russian vaccine, Sputnik.

None of these concerns with the drug regulator are new.

The abuse of the approval process

Approval for marketing of drugs and devices in the country is governed by the colonial era Drugs and Cosmetics Act, 1940 along with a series of byzantine regulations poorly drafted under this law. The agency which is tasked with administering this law and its rules is the Central Drugs Standards Control Organisation (CDSCO) headed by the DCGI.

The CDSCO has a sordid history of collusion with the industry and making marketing approval decisions based on anything but Science. The Parliamentary Standing Committee on Health in its 59th report, tabled in 2012, on the functioning of the drug regular had

said this:

> The extant Indian system is nowhere in so far as sheer competence and professional qualifications are concerned when compared with countries like USA and UK. There is sufficient evidence on record to conclude that there is collusive nexus between drug manufacturers, some functionaries of CDSCO and some medical experts.

The same report had this to say about the approvals provided to three drugs by the CDSCO:

> If the above cases are not enough to prove the apparent nexus that exists between drug manufacturers and many experts whose opinion matters so much in the decision making process at the CDSCO, nothing can be more outrageous than clinical trial approval given to the Fixed Dose Combination of aceclofenac with drotaverine which is not permitted in any developed country of North America, Europe or Australia. The Committee is of the view that responsibility needs to be fixed for unlawfully approving Buclizine, a drug of hardly any consequence to public health in India, more so since it is being administered to babies/children. The Committee recommends that in view of the unlawful approval granted to Deanxit, the matter should be re-visited and re-examined.

We pursued to unearth the documents and the data based on which the CDSCO provided these approvals using the Right to Information as our avenue. After stone-walling us for over two years, the CDSCO provided us a copy of the report of the Mohapatra Committee, which was established by the DCGI in 2013 to investigate the approval of the above drug. This report, which documents the approval the three drugs identified by the Parliamentary Standing Committee, assigns blame by singling out and naming former Drug Controller Generals of India. It says:

> The Committee finds that the DCGI was solely responsible for the irregularity noted by the Hon' Parliamentary Standing Committee in approving the aceclofenac with drotaverine combination. It names the then DCGI Dr. Surinder Singh saying "the claims of clinical trials were accepted just on their face value without any verification" …."an approval was granted". For the approval of Buclizine, the report says "The order of the DCGI ignoring statutory requirements under Schedule Y" …. "and the committee finds was arbitrary, whimsical and inconsistent with the provisions of the law"… "the Committee finds that the DCGI was solely responsible for the irregular approval of the drug".

In the case of Letrozole, the report says

> The case was a total misuse of the statutory and discretionary power by the DCGI and disregard for the statutory provisions and the observations and the suggestions of the immediate senior most officer of the system. Shri Aswini Kumar was the DCGI at that time of approval of the clinical trials and Dr. M. Venakteswarulu was the DCGI when the approval was granted.

Despite two sets of damning findings, one by the Parliamentary Standing Committee and the other by the government's own committee of experts, we have seen little comprehensive reform of the CDSCO and DCGI. It is as if no one in the Ministry of Health and Family Welfare or the Prime Minister's Office wants to look at this mess or have implicitly given their permission to the CDSCO to continue its charade.

Approval without adequate evidence

Access to good quality affordable medicines is a key component of public health in our country. A vast number of villages in rural India do not have access to a primary health centre. Those in districts are often poorly staffed and inadequately resourced. We rely on ASHA and Anganwadi workers who are not even paid a decent wage to ensure our children are vaccinated and our primary health outcomes for child mortality and maternal health are at least presentable.

The upper middle class and the elite do not worry about access to health; people with means and connections often prefer to get treated at privately run tertiary care centres or a premier government run institution like the All-India Institute of Medical Sciences (AIIMS), even if their ailment requires nothing more than what a primary healthcare centre offers. Yet drug regulation is one aspect of governance that affects all classes, although the poor feel a disproportionate impact of such incompetent governance.

This pandemic has shattered the complacency of the middle class that was comfortably assured that their ability to pay would get them access to treatment at a private facility. What we saw unfold in front of our eyes was despite their capacity to pay, in some cases lakhs of rupees for bed in a hospital, those were hard to come by. The same story played out with drugs like Favipiravir.

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The Covid-19 pandemic created a sense of urgency to treat those infected with a new disease and preliminary understanding of its progression and pathology; a number of countries and organizations began testing existing therapies to evaluate whether they were therapeutically effective in treating infections from Sars-CoV-2. The CDSCO provided "restricted emergency approval", whatever that means, under its authority to grant accelerated approvals pursuant to the New Drugs and Clinical Trial Rules, 2019 for a number of new drugs like Favipiravir, Itolizumab and Virafin.

The question one needs to ask is what, if any, was the clinical evidence and its robustness behind the approval of these drugs by the CDSCO. Enough has been written and argued that the evidence at best was flimsy for all these drugs; at worst, confirms the character of the drug regulator as described in the Parliamentary Standing Committee Report.

Wake-up call?

Historical evidence of the malfeasance of the central drug regulator is available in abundance for anyone to see. Sadly, until the advent of this epidemic, the collateral damage from its dysfunction and malpractice never registered in the consciousness of the large middle class in the country. Even in the past, the deaths of 12 children born to families that live below the poverty line, due to adulterated medicines, has hardly received any attention from the middle class.

This apathy has come home to roost during the pandemic. The fallacious decisions made by the CDSCO to approve questionable new drugs has had real consequence both in terms of spread of the infections to those who had to stand in long lines to buy these drugs with little to no clinical evidence of therapeutic benefit, and of an economic cost due to panic buying and rampant black marketing. Hopefully, the members of the entitled class will now wake up and hold the national drug regulator to account for all its malfeasance.