Source : www.livemint.com Date : 2022-01-18

# A COGNITIVE DISSONANCE IN DRUG REGULATION?

Relevant for: Science & Technology | Topic: Science and Technology- developments and their applications and effects in everyday life

**TORONTO** : On 14 January, about 33 leading public health experts, from institutes ranging from Mayo Clinic in the US to Manipal Hospitals in Bengaluru, shot off an open letter to state and central ministries of health, and to the Indian Medical Association.

The letter raised several issues, including the fact that expensive diagnostics and medications with limited evidence were being promoted in India.

“Despite the weight of this evidence and the crushing death toll of the delta wave, we find the mistakes of the 2021 response being repeated in 2022. We urge you to intervene to stop the use of medications and diagnostics that are inappropriate for the clinical management of covid-19," the signatories wrote. Particularly, the experts urged the government to discourage the use of “alternative therapies, potions, antibodies, ‘cocktails’, and drugs like molnupiravir, which are expected to be widely abused".

The letter came days after Balram Bhargava, the director general of the Indian Council of Medical Research (ICMR), India’s apex medical research body, also raised an alarm—again, over the use of molnupiravir. “The known and unknown risks of the drug outweigh its benefits," he commented.

The drug received emergency use approval from India’s drug regulator, the Central Drugs Standard Control Organization (CDSCO), as a treatment for mild and moderate covid-19 patients early in January, paving the way for eight Indian generic companies to launch the drug as the first line of treatment. CDSCO is headed by the Drugs Controller General of India (DCGI).

While molnupiravir is the latest flashpoint, as the opposition from experts show, this is not the first time the DCGI’s office has courted controversy. In the last two years, it has issued emergency approval to many drugs with limited evidence in improving the condition of covid-19 patients. On the other hand, ICMR’s national task force on covid management has remained conservative in endorsing several medicines that were given the emergency approvals.

In the context of India’s battle against the pandemic, ICMR’s opinion matters. Its task force issues covid-19 clinical guidelines that are supposed to be the guiding document on the treatment protocol for hospitals across the country. The team that reviews evidence on the new covid drugs has some of the leading physicians of the country, including Randeep Guleria, director of the All India Institute of Medical Sciences (AIIMS), and Raman Gangakhedkar, the former head of epidemiology at ICMR.

However, the differing views between the drugs controller and ICMR’s clinical guidelines is now hurting India’s covid-19 response, jeopardizing public health, several experts Mint spoke to said. The lack of coordination between the ICMR’s national task force and the drug controller’s office is leading to irrational drug use, confusion among the medical community and additional treatment cost to patients.

Some of the drugs approved by DCGI’s office and not endorsed by ICMR’s clinical guidelines have found their way to many private hospitals in the country. The average cost of hospitalization due to covid-19 in a private hospital can range anywhere between 50,000 and 2 lakh. The expensive covid-19 treatments are 40% of this cost, experts estimated.

“India needs rational use of drugs in the private and public sectors, especially during the pandemic. There cannot be two separate clinical guidelines," said Leena Menghaney, an activist working on the issue of access to medicines. “Once a drug is approved by the regulator, there is really no way to monitor how it is being administered," Menghaney added.

The lack of coordination is particularly unacceptable since the pandemic is two years old. A synchronized playbook—where the ICMR and the drugs controller work together—should have been in place.

“Covid in 2022 is way different than what it was in 2020. Two years ago, physicians had no idea what treatments work and hence there was some rationale in prescribing some of these drugs—simply because we did not have evidence either way," Dr Rajeev Jayadevan, a Kerala-based physician and one of the signatories of the open letter, said. “But now, we have clear evidence of what works and what doesn’t. It is no longer acceptable to prescribe some of these drugs, especially in asymptomatic or mild cases."

Emails to the drugs regulator and ICMR asking for comments on its approval processes remained unanswered.

Approval with caveats

Let us take a closer look at some of the drugs that have raised eyebrows. Molnupiravir, first.

Molnupiravir is a repurposed anti-viral drug by US drugmaker Merck and Ridgeback Biotherapeutics that works by introducing an “error" in the SARS Cov2 virus. That prevents its replication in the immune system. Ever since the drug went into a trial, it has courted controversy. The companies touted interim results—results in the middle of the trial—saying the drug showed over 70% efficacy in cutting hospitalization. After the initial euphoria, the drug failed to show significant improvement in moderate to severe covid-19 patients in the final trial. The relative risk reduction from hospitalization or death after using the drug was 30%. The advisory committee of the United States Food and Drug Administration (USFDA) was divided while approving the drug and it narrowly made it through with 13/10 votes. The approval, however, came with several caveats.

The USFDA, in a public statement, said that Molnupiravir is not authorized for use in patients younger than 18 years of age because it may affect bone and cartilage growth. It also said that the drug is not authorized for the pre-exposure or post-exposure prevention of coivd-19 or for initiation of treatment in patients hospitalized due to covid-19. Additionally, the drug is also not recommended to be used among pregnant women as in lab studies, the drug was shown to cause fetal harm.

Unlike the USFDA, the Indian drug regulator has not come up with any such advisory—instead, it asked the pharma companies to communicate the risks and side effects of the drug to physicians.

SP Kalantri, professor of Medicine, Mahatma Gandhi Institute of Medical Sciences, Sewagram, told Mint that given the rather small benefits in a highly selected population of the drug, there is a need for meticulous monitoring. “The ICMR has sounded caution in interpreting the findings and is perfectly justified in withholding the drug from the covid management protocol. The drug regulator seems to have acted a bit hastily in approving the drug," Kalantri said. “It is “absolutely necessary that the ICMR and the drug controller should work together while approving critical covid-19 drugs."

MSD (Merck in the USA & Canada), in an email response to Mint, defended the approval.

“The restrictive emergency use was granted to the eight generic manufacturers in India who have entered into voluntary licensing agreements with MSD. We provided relevant information as requested to help the DCGI determine the most appropriate use of molnupiravir in India," the company stated. “We are confident in the clinical profile of molnupiravir, which demonstrated a significant reduction in the risk of hospitalization or death in our phase 3 clinical trial with no observed safety concerns when compared to the placebo group," MSD added.

**Fast job**

What are the other drugs DCGI’s office approved that kicked up a controversy?

One was itolizumab, a monoclonal antibody that was launched at a price of 32,000 for four vials. It was approved in July 2020 based on a clinical trial done in 30 patients. Another commonly used covid-19 drug favipiravir was approved the same month. It suffers from inconclusive evidence, too.

Glenmark, the Mumbai-based pharma company that conducted the trial, said that the drug was “safe and effective". However, according to a study published in November 2020, in medical journal Elsevier, favipiravir did not have a statistically significant difference in a patient’s recovery. In November 2021, Appili Therapeutics, the Canadian clinical trial partner of Fujifilm (the Japanese company that discovered the molecule) reported that a study of the drug “did not achieve statistical significance for the primary endpoint of time to sustained clinical recovery" of mild to moderate patients. The trial enrolled 1,231 patients across US, Mexico and Brazil. In Japan, the drug is not recommended for covid-19 use and is prescribed as a flu medication.

Then, an antibody cocktail drug by US drugmaker Regeneron Pharmaceuticals, approved in India in May 2021 (famous because Donald Trump had received it), has also been approved by the drug controller. According to Regeneron, it is not effective against the Omicron variant.

“While Regeneron’s currently authorized REGEN-COV antibodies have diminished potency against Omicron, they are active against Delta, which currently is the most prevalent variant in the US," the company said in a statement on 16 December 2021. The USFDA, too, has revised its guideline and advised against the use of the drug as it is ineffective in the Omicron wave.

“Circulating SARS-CoV-2 viral variants, including Omicron, may be associated with resistance to monoclonal antibodies," said a statement from the US Department of Health and Human Services. Based on the information, the department decided to stop the allocation of this drug across healthcare facilities in the country. Despite emerging evidence such as this, the DCGI’s office has not issued any clarification on the use of the drug.

Like we mentioned earlier, some of the above-mentioned drugs have not been recommended by ICMR’s national task force due to a lack of evidence on clinical benefit.

The task force’s current guidelines prescribe a limited set of drugs for the treatment of covid-19. They include anti-asthma drug budesonide for mild patients, remdesevir for moderately ill patients, and tocilizumab in extreme cases. Nevertheless, during the initial days of the pandemic, the task force also recommended the use of hydroxychloroquine despite mounting evidence against the ineffectiveness of the drug.

Shrouded in secrecy

Meanwhile, the functioning of the Indian drugs controller's office remains opaque.

For instance, there is little information on the drug and vaccine approval processes for covid-19—on the evidence that were considered. The drugs controller is guided by a group known as the 'subject expert committee'. In the last two years, there has been little to no disclosure on the members approving covid-19 drugs and vaccines. According to past statements from the government, these members are "domain knowledge experts from the fields of pulmonology, immunology, microbiology, pharmacology, paediatrics, internal medicine, etc".

This sort of secrecy runs contrary to the practices of several other countries, including the USFDA, considered to be one of the stringiest regulators in the world. For example, before a drug is taken up for an approval, companies in the US have to make a public presentation to an independent panel of experts on the product. This presentation is open to public. During the pandemic months, the presentations were made over video conferences and anyone could have been present online. Once a drug is approved for emergency use, the USFDA releases a detailed statement on the uses of the drug, the side effects, and its effect on various population groups. This is backed with several scientific papers that support the rationale behind the approval.

It is high time the Indian drugs regulator makes similar lengthy disclosures. And naming the members of the subject matter committee could be a good beginning.

"It is no secret that the drugs controller's office was under tremendous pressure from pharma companies to approve certain drugs. But, during the pandemic, it cannot be business as usual," Leena Menghaney, the activist, said.

Opaque decision-making hurts public health especially since most Indians pay out of their pockets, she added.



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