Citizens for Affordable,
Safe & Effective Medicine
CASEM

To,

August 29, 2020

Dr. Harsh Vardhan
Minister for Health & Family Welfare,
Government of India,
348-A, Nirman Bhawan,
Maulana Azad Road,
New Delhi – 110 011.

Dear Sir,

Sub: Petition requesting transparency in the investigation and recall of DEG contaminated cough syrup that has killed 12 children

1. By way of introduction, I am a public health activist and the Founder of Citizens for Affordable, Safe & Effective Medicine (CASEM) which aims to be a collective of like- minded individuals working towards ensuring that the medicines supplied to India and other countries are affordable, safe and effective. I have formerly worked in the Indian pharmaceutical industry and was responsible for exposing the regulatory violations at Ranbaxy Laboratories after which the company was prosecuted and fined $500 million dollars by the United States Food and Drug Administration (USFDA).[1] Since the end of my whistleblower lawsuit against Ranbaxy in 2013, I have been engaged in advocacy aimed at strengthening the drug regulatory framework in India. This includes a report that I submitted to the Ministry on measures to improve drug regulation in India[2], a petition to the Prime Minister's Office[3] requesting a prohibition on certain harmful drugs, as well as an ongoing writ petition before the Delhi High Court[4] requesting directions to the

[1] 'Ranbaxy pleads guilty, to pay $500 mln in settlement', *Reuters*, May 13, 2013.
[2] Dinesh Thakur & Prashant Reddy, 'A report on fixing India's broken drug regulatory framework' (June, 2016) *available here*: ; https://dineshthakur.com/wp-content/uploads/2016/06/CDSCO-Reform.pdf Dinesh Thakur, 'India needs strict prosecution laws to fix drug regulatory system: Ranbaxy whistleblower Dinesh Thakur', *Economic Times,* June 24, 2016.
[3] Prabha Raghavan, 'Ranbaxy whistleblower petitions PMO to investigate 'illegal' drug approvals', *Economic Times*, May 21, 2018. The text of the petition can be accessed over here: https://dineshthakur.com/wp-content/uploads/2018/05/Petition-to-the-Prime-Minister.pdf
[4] Dinesh Thakur v. Union of India, W.P. No. 11107 of 2018 before the High Court of Delhi at New Delhi.

100 1st Ave North, Ste 3603
St. Petersburg, FL 33701 USA
contact@casemindia.org

Central Government to prohibit certain drugs that were red flagged by a Parliamentary Standing Committee on Health. Over the course of the last year I have also petitioned the government to relook bioequivalence and stability norms, sampling and testing norms, as well as increased transparency in drug regulation.

2. We are writing to you with regard to the inadequate and opaque investigations being conducted by the Himachal Pradesh Drug Control Administration (HPDCA) and the Central Drugs Standards Control Organisation (CDSCO) into the pharmaceutical manufacturer Digital Vision, for its alleged role in the manufacture and sale of adulterated cough syrups.

3. The first case of adulteration was discovered in February this year after the deaths of 12 children from the Ramnagar area of Udhampur, Jammu. It has been alleged by several media reports, that those deaths were caused by a cough syrup sold manufactured and sold by Digital Vision, under the brand name COLDBEST. This syrup is a fixed dose combination of Paracetamol, Phenylephrine Hydrochloride and Chlorpheniramine Maleate. As per preliminary reports, the COLDBEST cough syrup was allegedly contaminated by diethylene glycol (DEG), which is an anti-freeze agent that can be fatal when consumed by humans.[5] The cause of contamination appears to be a batch of propylene glycol (PG) that was procured from an unlicensed chemical trader. This batch of propylene glycol was alleged to have been contaminated with DEG. The impurity would have been detected if the manufacturer had tested the PG before using it to manufacture the cough syrup.

4. A few weeks ago (and more than 6 months after the 12 deaths), the media reported yet another instance of DEG poisoning of an infant causing renal failure. As per a report from PGIMER, the child had allegedly consumed COFSET-AT cough syrup manufactured by Digital Vision. This cough syrup is reportedly a fixed dose

[5] Sushil Manav, 'How syrup to cure cold, fever proved fatal for kids', *Tribune India* March 1, 2020 *available at* https://www.tribuneindia.com/news/features/how-syrup-to-cure-cold-fever-proved-fatal-for-kids-49200.

combination of Ambroxol Hydrochloride, Terabutaline Sulphate, Guaiphenesin, Menthol). The sample of COFSET-AT sent for testing by PGIMER allegedly showed traces for diethylene glycol (DEG), the same contaminant that was alleged to have been found in the COLDBEST case.[6] The fact that two different brands of cough syrup manufactured by the same company have alleged tested positive for the same contaminant, a few months apart, is shocking and raises serious questions about regulatory accountability. In particular we would like to point out three shocking irregularities that have come to light. These are explained in detail below.

A. <u>The non-maintenance of stock registers</u>

5. The most likely, but yet to be confirmed reason, for both COLDBEST and COFSET-AT testing positive for DEG, is that both formulations were manufactured using the same batch of propylene glycol (PG), contaminated with DEG, that was procured from a Chandigarh based chemical trader called Thakur Enterprises.

6. It worries us that the regulatory authorities were unable to track all the DEG contaminated formulations that were manufactured by Digital Vision at the time of the first inspection in February when the first deaths were traced to Digital Vision. If there are more such contaminated batches and formulations out in the market there is a possibility of a massive but silent public health crisis taking place because DEG poisoning is not easy for doctors to detect. It is very likely that there are several unreported deaths due to these cough syrup formulations where doctors have not been able to trace the poisoning to the contaminated cough syrups.

7. We suspect that the main reason that the CDSCO and the HPDCA have been unable to account for all the contaminated batches is because of poor record keeping

[6] Usha Sharma, 'DCGI asks drug controllers to prevent sale, distribution of DEG contaminated cough syrup, COFSET', *Express Pharma* August 7, 2020 *available at* https://www.expresspharma.in/latest-updates/dcgi-asks-drug-controllers-to-prevent-sale-distribution-of-deg-contaminated-cough-syrup-cofset/.

practices at Digital Vision. We learnt of this fact from a judgment delivered by the High Court of Himachal Pradesh in a case involving Digital Vision.[7] The court records the following submissions of the Regulatory Authority:

"On 17.02.2020, the Drug Inspector, Nahan directed the petitioner to produce certain specified record including stock registers reflecting use of PG. Petitioner vide its communication of even date, **expressed its inability to produce the desired record** that day and stated that the same can be made available in three days. Observing that record was immediately required by the investigation team specially constituted by the respondents, the Assistant Drugs Controller-cum-Drugs Licensing Authority, Nahan, 'keeping in view the seriousness of the matter in public interest' on 17.02.2020, issued a show cause notice-cum-stop manufacturing order to the petitioner in respect of its Drug Manufacturing Licenses. **The show cause notice was issued with respect to not producing the desired record.**" (emphasis supplied)

8. If these above submissions are in fact accurate and Digital Vision did not maintain accurate stock registers identifying the batch numbers and formulations using the contaminated PG, then there is no possible way for the regulators to identify the batch numbers and formulations which were manufactured using the adulterated DEG. In this backdrop, there is a very serious possibility that there are several batches of several different formulations produced by Digital Vision which are contaminated with DEG that are still available in the market.

B. The lack of testing equipment at Digital Vision

9. A second fact that we learnt from the aforementioned judgment of the High Court was that Digital Vision lacked basic testing equipment required for testing the PG batches procured from outside supplier. The judgment records the following submission from the regulator:

"**However, admittedly the petitioner-firm does not possess the testing facility for checking its drugs formulations for presence of adulterant DEG**. Therefore, analysis

[7] Digital Vision v. State of Himachal Pradesh CWP No. 2572 of 2020 delivered on August 14, 2020 *available at* https://indiankanoon.org/doc/115798745/

reports of petitioner's Quality Control Department with respect to COLDBEST-PC Syrup cannot be relied upon. Same goes for test reports of petitioner's Quality Control Department with respect to analysis of sample of PG. It cannot be said to have been tested for presence of poisonous adulterant DEG in absence of such testing facility available with the petitioner." (emphasis supplied)

10. The fact that Digital Vision did not have the equipment to test its formulations for DEG is a prima facie violation of the Goof Manufacturing Requirements (GMPs) outlined in Schedule M to the Drugs & Cosmetics Act.[8] It is shocking that the firm was allowed to be in business for so long despite lacking minimum testing equipment. Given that the company has failed to test for a well-known impurity like DEG in PG, one can only wonder as to the state of the rest of its manufacturing practices. Despite these known defects, the HPDCA failed to convince the High Court that it was necessary to stop Digital Vision from manufacturing any products. In the aforementioned judgment, the High Court has maintained the ban on Digital Vision manufacturing any formulations using PG but has set aside the ban order on the other formulations because the HPDCA failed to make out a convincing case for sustaining the ban. This failure to convince the court reflects very poorly on the regulatory authority.

C. <u>Digital Vision's track record of manufacturing sub-standard drugs</u>

11. In addition, we would like to point out that as per the XLN database of substandard drugs detected by drug inspectors from 12 different states, there have been 13 instances where formulations manufactured by Digital Vision have been declared

[8] Section 10 of Schedule M states: 10.9 Only raw materials which have been released by the Quality Control Department and which are within their shelf-life shall be used. It shall be ensured that shelf life of formulation product shall not exceed with that of active raw materials used. 15.1 To evaluate the manufacturer ís compliance with GMP in all aspects of production and quality control, concept of self-inspection shall be followed. The manufacturer shall constitute a team of independent, experienced, qualified persons from within or outside the company, who can audit objectively the implementation of methodology and procedures evolved. The procedure for self-inspection shall be documented indicating self-inspection results; evaluation, conclusions and recommended corrective actions with effective follow up program. The recommendations for corrective action shall be adopted.

16.6 No batch of the product shall be released for sale or supply until it has been certified by the authorized person(s) that it is in accordance with the requirements of the standards laid down.

substandard by various state government drug laboratories. These quality failures are spectacular. In some cases the active ingredient in the sample tested as low as 8.68% and17.3% of the amount advertised on the label. In other cases, the samples failed disintegration and dissolution tests. A snapshot of the database, listing Digital Vision's substandard formulations is annexed to this petition. We presume that the HPDCA inspected Digital Vision's plant in past instances and it is surprising that none of the glaring violations of GMP were caught earlier by the drug inspectors.

D. Prayers

12. The three irregularities mentioned above are indicators of a major regulatory failure and one that can lead to a public health crisis. In these circumstances we request the Health Ministry to order the CDSCO to put into the public domain the following information pertaining to the recall of contaminated syrups as well as the investigation into the failures at Digital Vision:

(a) Ensure transparency regarding all pharmaceutical companies that have procured PG from Thakur Enterprises: Given that the source of contaminated PG used by Digital Vision has been tracked to Thakur Enterprises it is necessary for regulators to identify and make public the names of all other pharmaceutical companies that may have sourced PG from the same manufacture. Such an exercise will help identify other cases of possible DEG contamination because of other manufacturers who have used the PG in a similar manner without testing it, or the final product for DEG contamination.

(b) Transparency regarding the formulations manufactured by Digital Vision that used PG and the status of the recall: Till date, neither the CDSCO nor the HPDCA have made public the formulations and batch numbers of products manufactured at Digital Vision using PG. There is no such information available on the websites of either the CDSCO or the HPDCA. Given that a

second brand from the same company has been found to have the same contaminant, the regulators should put out a list of all products manufactured at Digital Vision using PG. Ideally, if Digital Vision maintained an accurate stock register it would have been possible to identify the precise batches for which the contaminated PG has been used then only the contaminated batches could have been recalled. Since the company allegedly did not maintain an accurate stock register, it follows that any formulation manufactured at Digital Vision, where propylene glycol was an ingredient, is now a high-risk product that needs to be recalled from the market. A good first step therefore is to identify all formulations that used propylene glycol as an ingredient in the manufacturing process. Any such list of formulations should be publicly advertised on the website of the CDSCO and then recalled.

(c) Releasing inspection reports: So far, neither the CDSCO and HPDCA have publicly released any of the inspection reports of Digital Vision's manufacturing plant. The only details that we able to learn about the inspection reports are those which have been reproduced in the judgment of the High Court. This is unacceptable. Citizens have the right to be informed of the manufacturing practices of pharmaceutical companies suspected of producing contaminated cough syrup so that they can understand what exactly went wrong and pose questions to the regulators about why they failed to discharge their regulatory duty. The regulators should therefore be directed to make public the inspection report of Digital Vision's manufacturing plant.

(d) Making public the recall strategy employed by the CDSCO in this case: The recall procedure followed by the CDSCO to withdraw COLDBEST products from across different states has been shrouded in utter secrecy. The DCGI appears to have written letters to state regulatory authorities but that is insufficient to affect an effective recall in a country like India. In most countries, a public recall will be accompanied by an effective media strategy, which should include announcements and advertisements in newspapers, on the radio and the television. None of these strategies were adopted by the

CDSCO because it does not have in place any standard procedure to oversee national recalls. At the very least, the CDSCO must be directed to publish for public comments a recall strategy for the contaminated formulations that Digital Vision has allegedly manufactured and marketed.

(e) A transparent accounting of all recalls: In addition to publishing the recall strategy, the CDSCO must also be required to regularly update the public on the number of bottles of the suspected batches that have been recalled and from which district of the court. Such information will undoubtedly help inform doctors and the public of the main locations of sale of the contaminated cough syrup. This will help them take better precautions.

(f) Examining the manner in which HPDCA has investigated previous cases of quality failures at Digital Vision: As we have mentioned earlier, the XLN database lists 13 instances of Digital Vision having been accused of manufacturing sub-standard medicines. In addition, it appears from the High Court judgments that Digital Vision was found lacking in testing equipment as well as following poor documentation practices. Given this track record, it is astonishing that Digital Vision was allowed to manufacture drugs for so long. The Health Ministry must initiate an exercise to publish the past inspections reports of the HPDCA so that citizens can understand the manner in which the HPDCA has failed to carry out its regulatory functions.

13. We trust and hope the government will treat this petition with the urgency and speed that the situation demands. If required, I can be contacted at dinesh@casemindia.org.

Best Regards,

Dinesh Thakur,
Founder, CASEM

100 1st Ave North, Ste 3603
St. Petersburg, FL 33701 USA
contact@casemindia.org