Citizens for Affordable,
Safe & Effective Medicine
CASEM

To,

July 3, 2020

Dr. Harshavardhan
Union Minister for Health,
Government of India,
348-A, Nirman Bhavan,
Maulana Azad Road,
New Delhi – 110011.
Email: hfm@gov.in

Dear Minister,

Petition to setup Expert Committee to examine the sampling and testing protocols of drugs withdrawn under Section 23 & Section 25 of the Drugs & Cosmetics Act, 1940

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 Central Government to prohibit certain drugs that were red flagged by a Parliamentary Standing Committee on Health.

2. On behalf of CASEM, I kindly request you to please consider favourably our petition requesting the setting up of an Expert Committee to re-examine the sampling and

[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.

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testing protocols under the Drugs & Cosmetics Act, 1940. In the normal course, Drug Inspectors are required to draw samples of drugs from the market and send these samples to a Government Analyst who is required to test these samples as per the standards recognized in the Second Schedule to the Drug & Cosmetics Act. The prevailing standard is usually the Indian Pharmacopeia (IP) which has been prepared by the Indian Pharmacopeia Commission (IPC), which is a government body. However, in certain cases, manufacturers are also allowed to prepare their formulations as per the American (USP) or British (BP) Pharmacopeias where a monograph is not available in the IP. The choice of the pharmacopeia used by the Government Analyst depends on the labeling of the drug, where the manufacturer mentions the pharmacopeia that should be used as a reference for testing. As per Section 25, after the testing is completed, the Government Analyst is required to send the test report to the Drug Inspector who may then make a decision whether to prosecute the manufacturer if the drug fails testing.

3. In our opinion, the above procedure which was laid down in 1940 is antiquated for the reasons that we highlight in this petition. The most important reason is that the current sampling and testing protocols do not provide an adequate means to conduct surveillance of the pharmaceutical supply chain in India.

A. Sampling Protocols

4. As per Section 23 of the Drugs & Cosmetics Act, 1940 the Drug Inspector is required to draw 3 to 4 samples of the same drug from the market. Once drawn from the market, after tendering a fair price for the purchase, these samples are 'sealed' in order to prevent tampering. Of these, one sealed sample is returned to the person from where it was drawn, one is produced in court and the last is sent to the manufacturer of the drug. Thereafter one of the sealed samples is sent to the Government Analyst in a State Drug Laboratory for testing. If the sample fails the prescribed test, depending on whether it is sub-standard or misbranded or adulterated, a prosecution maybe initiated by the Drug Inspector before a criminal court.

5. In our opinion there are two problems with how drugs are sampled by the Drug Inspectors from the market.

6. The first problem is the complete absence of any scientific sampling guidelines to guide Drug Inspectors on the kind of drugs, location of sampling and the type of manufacturers that should be the focus of sampling. Some states and the CDSCO do have vague guidelines which require 5 drugs to be drawn, every month, from government dispensaries, hospitals, rural outlets and from manufacturing premises but awareness of even these vague guidelines is low amongst most Drug Inspectors. These vague guidelines do not provide any guidance on the categories of drugs/manufacturers that should be sampled. Since the sampling process is left to the discretion of individual Drug Inspectors, it is possible that some categories of drugs maybe under represented while other categories will be over represented. We also suspect that these decisions maybe swayed by the budgets available for the department because Drug Inspectors are required to tender a fair price while purchasing samples from the market. If budgets are limited and Drug Inspectors are expected to meet a quota of 20 samples , they may end up purchasing only those drugs that fit within their budgets.[5] This does not serve the purpose of adequately monitoring the quality of drugs being sold in the relevant market.

7. The second problem with current mode of drawing samples from the market is the statutory insistence, in Section 23, on the Drugs Inspector drawing only 3 or 4 samples of which only 1 sample is sent to the Government Analyst for testing. The success or failure of merely 1 sample out of an entire batch (which could be anywhere between 500 to 2000 units) is statistically irrelevant in our opinion and does not really provide enough information to conclude the robustness or otherwise of the manufacturing process followed by a pharmaceutical company. It may be relevant to point out that even the Indian Pharmacopeia (IP) which is an official Government publication, stresses on the importance of testing a statistically significant sample of a batch. In pertinent part, it states the following: "Assurance of quality must be ensured by the manufacturer by the use of statistically valid sampling and testing programmes."[6] The above assertion, while made in the context of self-testing by manufacturers during their internal quality assurance program, is relevant even for sampling that takes place for the purpose of law

[5] Information regarding budgets for sampling of drugs from the market is not easily available. Information provided by the drug regulatory authority in Kerala in reply to RTI applications indicated that the budgets varied from Rs. 12,500 to Rs. 1,13,800 for the year 2013-14 depending on the drug inspector and zone.
[6] IP 2010, Vol 1 – Page 14.

enforcement. It would be a far better solution for the Drug Inspector to draw samples in a statistically relevant manner that is based on the batch size.

8. In our opinion, it would be in public interest for the Health Ministry to set up an expert committee to study this issue and if required suggest an amendment to the Drugs & Cosmetics Act to ensure that any kind of market sampling is based on statistically significant models.

B. Testing Protocols

9. The second issue in our petition is the manner in which samples sent to the Government Analyst are tested in government laboratories. As explained earlier, the Second Schedule to the Drugs & Cosmetics Act officially recognizes the Indian Pharmacopeia (IP) along with the British and American Pharmacopeia as laying down the standards for testing whether manufactured drugs are of standard quality. These Pharmacopeias consist of individual monographs for each and every drug that is sold in the market. Depending on the formulation, a series of tests and their respective methods are prescribed for each drug. The most common test across formulations is the assay test which determines the amount of the active ingredient present in the formulation and whether it matches the amount advertised on the label of the drug. For certain formulations like creams or syrups, additional tests for endotoxins and sterility have to be conducted, while tablets are tested for their weight and their ability to disintegrate in solutions with a prescribed pH value.

10. We have three specific concerns regarding the testing protocols followed by government laboratories in India.

11. Our first concern is regarding the reliance on only the IP while testing drug samples for their quality. It should be noted that even the IP notes that "Pharmacopoeial methods and limits should be used merely as compliance requirements and not as requirements to guarantee total quality assurance".[7] In other words, if the aim is to conduct a comprehensive quality check of drugs, there is a need to go beyond the testing protocols prescribed in the IP. We believe that the only way to conduct a comprehensive quality check is to complement the testing of drug samples in government laboratories with a

[7] IP 2010 Vol 1 – page 14.

dedicated audit of the batch records at the manufacturer's facility in order to assess whether the pharmaceutical company has complied with mandatory batch release testing, as specified in Schedule M. This is especially important given the number of inspections by the United States Food & Drugs Administration (USFDA) of Indian pharmaceutical plants that have revealed large scale fabrication of safety data records. Any decision on prosecution should be based on a combination of the test report of the commercial sampling as well as scrutiny of the internal batch testing records at the manufacturing site. As of now, there is no such mandatory requirement under Indian law, although it may be possible that some Drug Inspectors may be conducting such inspections of the manufacturer's facilities of their own accord.

12. Our second concern is regarding the absence of testing for the impurity profile of a drug. We have come across several test reports from Government Analysts noting how visual examination of tablets or oral suspensions or oral solutions revealed discolouration of the tablets or black particles in the suspension or black coloured fungus growth in the containers. In all these cases, the drug is declared to be not of standard quality (NSQ) by the Government Analyst. The discolouration, black particles or black coloured fungus growth are signs of either an unstable drug breaking down or contamination due to bacteria or other impurities. There will however also be several cases where drugs may get contaminated or break down because of poor formulation and manufacturing practices without leaving visual cues such as discolouration or black particles. It is therefore important that government analysts not depend solely on visual cues to try and spot issues related to quality of the drugs whose samples they analyze. While there are specific tests used to detect bacterial contamination which are conducted by government laboratories in India if prescribed in the IP, the same laboratories are not conducting these tests to detect non-bacterial impurities. It is possible to detect and identify such impurities through standard analytical methods such as high performance liquid chromatography or spectroscopy.

13. It is important for government laboratories to detect and identify both visual and non-visual impurities because some of these impurities may be dangerous to patients. Only if government laboratories detect the impurities in question will they be in a position to alert Drug Inspectors who can affect a recall of these NSQ drugs from the market. If the impurities in question have the potential to cause 'grievous hurt' to patients, Section 27

of the Drugs & Cosmetics Act requires a harsher penalty to be imposed on the manufacturer. However without government laboratories scrutinizing these samples for impurities, there is no way for Drug Inspectors to seek harsher penalties against negligent manufacturers as required by the law. The equipment to test for such impurities is available in government laboratories but there must also be a legal requirement for government laboratories to conduct such testing which is currently missing. It would therefore be necessary to introduce a legal rule to mandate testing for impurities.

14. Our third concern regarding testing protocols is the testing of fixed dose combination (FDC) drug samples based on manufacturer supplied monographs. It is widely known that the Indian market is flooded with dangerous irrational FDCs that were approved by State Licensing Authorities (SLAs) despite not having any powers to do so. The Central Government had to step in to ban several hundred of these FDCs from the market. Despite the ban, several hundred FDCs continue to be sold in the Indian market. One of the problems with these FDCs is the absence of monographs in the IP to instruct the Government Analysts on how exactly they are to test the FDC sample in question for compliance with quality standards. Since the IP does not have this information, government analysts have to procure testing protocols from the manufacturers of these FDCs to test the drugs samples manufactured by these companies. It is not clear as to the extent to which these testing protocols are rigorously vetted from a scientific point of view. We have come across test reports from Government Analysts wherein the Government Analyst has stated that the test protocol provided by the manufacturer was "unworkable". In our opinion, this is a very serious issue and the government must amend the law to bar the manufacture of any FDC unless the Indian Pharmacopeia Commission (IPC) includes monographs for FDCs in the IP. Without established standards that have been independently validated by the IPC, there is no way to guarantee the quality of a FDC drug. This is absolutely crucial for Government Analysts to be able to guarantee the quality of FDCs and in the process protect public health.

15. In light of the above arguments, we request the constitution of an Expert Committee to study the following issues in greater detail and recommend changes to the law:

(a) Is there a requirement to draw up scientific guidelines to guide the sampling procedures under Section 23 of the Drugs & Cosmetics Act?

(b) Should Government Analysts be required to inspect the manufacturing records of every sample which is being tested in a government laboratory?

(c) Should the law be amended to mandatorily require Government Analysts to test all drugs for impurity profiles using appropriate analytical techniques such as HPLC, GC and MS?

(d) Should licensing authorities restrain the sale of fixed dose combinations until the Indian Pharmacopeia Commission is able to validate the monographs that lays down the testing protocol for Government Analysts?

16. 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