Citizens for Affordable,
Safe & Effective Medicine
CASEM

To,

June 7, 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 amend the framework put in place by the Drugs & Cosmetics (Third Amendment) Rules, 2018 for stability testing of drugs

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.

[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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2. On behalf of CASEM, I kindly request you to please consider favourably, our petition to setup an Expert Committee to relook the existing law on stability testing for both new drugs and generic drugs in India. Stability testing is very important to ensure that drugs being sold are manufactured as per the specifications and are unlikely to degrade due to heat, light or humidity. Drugs that degrade during their validity period (before their stated expiry date) do not deliver their intended therapeutic benefit; rather, products of such degradation, often cause adverse events in the patients who consume them. For most of Indian history, stability testing was not compulsory for most drugs. While the law was recently amended to make stability testing compulsory for all drugs, the law does not offer adequate guidance on the manner in which such stability testing ought to be conducted. Unless there is clarity on how these mandatory requirements are to be enforced, it is possible that each of the state licensing authorities will interpret these guidelines differently leading to inconsistent interpretations across the country.

3. In this petition, we at CASEM will present a case highlighting the importance of stability testing in ensuring the quality of our drug supply and the present lacunae in the Indian legal framework for stability testing. The petition ends with our recommendations on reforming Indian law on stability testing.

A. The Importance of Stability Testing in Ensuring Quality of Drugs

4. The process of manufacturing drugs, involves a complicated manufacturing process, starting with the manufacture of the Active Pharmaceutical Ingredient (API) in bulk. Once the API has been manufactured by a bulk drugs manufacturer, it is then procured by different companies, who will then formulate the API into different dosage forms such as tablets, capsules, syrups, injectibles etc. The final formulation is shipped to pharmacists and hospitals from whom, patients purchase the tablet or capsule and either consume it immediately or store it for future use. Very often, the entire journey from raw materials to reaching the

consumer's medicine cabinet in the shape of a pill will take place over a global supply chain that traverses many countries or perhaps continents.

5. Maintaining the stability of the drug throughout this journey is challenging because there is a potential for a poorly formulated drug to degrade at various points across the supply chain. The process of formulation involves mixing the API with excipients, which are chemicals that create the finished dosage form. Binders are added to increase adhesion among the molecules of the API to shape it into a tablet or a capsule. Flavor is added to ensure that children take their syrup because without the added flavor, the medicine may be unpalatable to consume. Such additives, called excipients in the industry also have similar liabilities when stored in conditions which are not hospitable. They too may degrade. Finally, products of degradation may cross-react with each other. For example, 'wax' which is used as a binder may degrade into oil at high temperatures. Oil turns rancid over time if not properly stored. Rancid oil then reacts with the active ingredients to generate chemical substances which may cause unintended consequences when consumed by patients. Likewise, most liquid formulations and syrups have instructions to "shake well before use" because the API/excipients may precipitate while being stored and settle at the bottom of the bottle. Shaking the syrup of the liquid formulation will help disperse the API/excipients into the medium. Poorly formulated liquid formulations may not re-dissolve into the medium (the liquid) making the drug formulation ineffective. Finally, some chemicals are photosensitive because of which they may degrade in presence of sunlight. Exposure of such API to direct sunlight/UV rays catalyzes a chemical reaction thereby degrading the API into constituent chemicals. These degraded chemicals do not have the therapeutic efficacy of the original API thereby making the drug product therapeutically ineffective.

6. It is a serious challenge for manufacturers to ensure that both the API and final formulation maintain their integrity and efficacy over the course of movement throughout a global supply chain. Degradations of these drugs due to stability

related issues can result in the loss of active ingredients, loss of bioavailability, differences in visual appearances and presence of impurities. In most cases, such degradation will mean a loss in efficacy of the drug meaning that the drug will no longer have the expected therapeutic impact on a patient. In a smaller minority of cases, the degradation of a drug, may lead to the formulation of dangerous impurities in the drug, which may be detrimental to the health of the patient through adverse events. For example, it was recently discovered that commonly used anti-acid, ranitidine, was inherently unstable in long term storage conditions leading to the formation of small amounts of a carcinogen called N-nitrosodimethylamine, or NDMA.[5] In most cases, unless there are visible changes to the appearance of a pill, patients will not be aware that the stability of the drug has been impacted and that it may have lost its therapeutic efficacy.

7. In order to ensure that pharmaceutical companies manufacture drugs that are stable in expected atmospheric conditions, most countries prescribe specific regulations regarding the stability parameters that are to be met by different types of drugs. Most of these regulations are based on an international consensus, under the umbrella of the International Conference on Harmonisation (ICH), wherein the world has been divided into four climatic zones based on temperature and humidity: Temperate (Zone I), Subtropical and Mediterranean (Zone II), Hot and Dry (Zone III), Hot and Humid (Zone IVa) and finally, Hot and Very Humid (Zone IVb). These zones provide international guidance to countries on defining their stability requirements. India for example has communicated to the WHO that it is adopting a 30°C/70% RH requirement, therefore putting it in between Zone III and IV requirements.[6] The expiry date on the packaging of pharmaceutical drugs usually indicates the expected time for

[5] Katie Thomas, 'Zantac Recall Widens as Sanofi Pulls Its Drug Over Carcinogen Fears', *New York Times* October 18, 2019 *available at* https://www.nytimes.com/2019/10/18/health/zantac-recall-carcinogen-sanofi.html

[6] Annex 2 – Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products, WHO Technical Report Series, No. 953, 2009; Also see Gireesh Babu, 'Long term stability test condition for India is 30°C/70%RH: NIPER study', *Pharmabiz* December 31, 2007 *available at* http://www.pharmabiz.com/NewsDetails.aspx?aid=42683&sid=2.

which a particular batch of pharmaceutical drugs is expected to remain stable and efficacious under these prevailing conditions across the country.

8. In order to ensure, that pharmaceutical companies ship only stable drugs to the market, most jurisdictions require them to conduct a series of stress tests, starting from right before shipping the batch to the market and continuing it at regular intervals till the stated life-cycle of the batch has been completed. These stress tests involve exposing a sample of drugs from each batch to the various elements such as heat, humidity and light. These tests are to be conducted in temperature/humidity controlled chambers which may also have facilities for UV light exposure. If the samples degrade when subjected to tests in these chambers, it is an indication of a faulty manufacturing process. Legally speaking, in most countries, if the stability testing reveals a flawed batch, it is incumbent on the manufacturer to either destroy the batch before it reaches the market, or in the case of long term testing conducted after the batch is already in the market, ensure that the failed batches are recalled from the market and destroyed.

9. Since such stability testing is an in-house process, with the pharmaceutical company checking its own products' stability, there is a significant incentive to game the system by either fabricating or manipulating stability data every time a batch fails stability testing. This is because destroying a batch can result in significant financial loss, while a batch recall from the market can involve both a financial and reputational loss. Several of the charges to which Ranbaxy pled guilty to before an American court, related to either a failure to conduct stability testing or cases where stability testing was conducted and a batch was not withdrawn from the market despite it failing the stability testing.[7] The position under Indian law regarding stability testing has been very different from the

[7] Plea Agreement between the Department of Justice, United States and Ranbaxy USA Inc. in the case of United States v. Ranbaxy Inc. dated January 2, 2013 *available at* https://dineshthakur.com/wp-content/uploads/2013/05/2013.05.13-Ranbaxy-Plea-Agreement.pdf.

international benchmark because of which most generic drugs in India have not been subject to the requirement of stability testing.

B. <u>The Evolution of Indian Law regarding Stability Testing</u>

10. Historically, the Indian law on stability testing differed for "new drugs" which are approved by the Central Licensing Authority (CLA) and other generic drugs which are approved by individual State Licensing Authorities (SLA). Under Indian law a drug maintains a "new drug" status for the first 4 years after it has been approved by the CLA for the Indian market.[8] After the 4 year period is crossed, other generic manufacturers can file their applications with SLAs rather than CLAs. To illustrate with an example, if a drug called "Elixir" was approved by the CLA for the first ever for the Indian market on January 1, 2016, the drug would have maintained its new drug status for 4 years till January 1, 2020. Those manufacturers who are producing generic versions of "Elixir" after January 1, 2020 are required to approach the SLA for licenses. Under the Drugs & Cosmetics Rules, 1945 the quality control standards have always differed for manufacturers of "new drugs" and those that enter the market after the 4 years milestone for "new drugs". The latter category usually has to submit lesser regulatory data to get an approval.

11. While it makes sense to abbreviate some data requirements (as is done with bioequivalence data) for generic drugs entering the market after the new drug, it has never been clear as to why the Drugs & Cosmetics Rules, 1945 did away with the "stability data" requirements for generic drugs entering the market after the expiry of the "new drug" status. As per Appendix IX to Schedule Y to the Drugs & Cosmetics Rules, 1945 any application for a "new drug" was to be accompanied by stability data. In 2019, the Government of India passed the New Drugs and Clinical Trial Rules, 2019 that lay down a new pathway to approve "new drugs". The Second Schedule to these Rules lays down the new stability testing

[8] Originally defined in Rule 122E of the Drugs & Cosmetics Rules, 1945 this definition has been replaced by Rule 2(w) of the New Drugs and Clinical Trial Rules, 2019. The definition remains substantially the same save for two categories of new drugs.

guidelines for "new drugs", whether in the form of a "drug substance" or "a formulation".

12. Before 2018, these rules did not make stability testing compulsory for generics entering the market after losing their new drug status. The decision to make "stability testing" compulsory in 2018 was preceded by almost 5 years of push and pull between expert committees and the pharmaceutical industry, which presumably did its best to resist attempts against the imposition of higher quality control standards. It is important to trace this 5 year journey to make stability testing mandatory, in order to establish the lethargy of the government and the significant pushback from the generic pharmaceutical industry which was putting profits ahead of quality.

13. The efforts to make stability testing compulsory for all generics began in 2013, at the 46th meeting of the Drugs Consultative Committee (DCC), comprising of state drug controllers. At this meeting, it was noted that the lack of mandatory stability testing for all generic drugs entering the market was a "serious lacuna" in Indian law. At the same meeting, the DCC "agreed that it is necessary that evidence and data of the stability of the drug products proposed to be manufactured by the licensee are required to be submitted to the regulatory authorities so as to ensure the stability of the drug formulations licensed in the country by the State Licensing Authorities."[9] A proposal on these lines, to the Drugs and Cosmetics Rules, 1945 was approved by the DCC and the same was agreed to even by the Drugs and Technical Advisory Board (DTAB) at its 65th meeting held a few weeks later.[10]

[9] Report of the 46th Meeting of the Drugs Consultative Committee held on 12th and 13th November, 2013 at New Delhi at p. 28 *available at* https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/common_download.jsp?num_id_pk=ODA4.

[10] Report of the 65th Meeting of the Drugs Technical Advisory Board (DTAB) held on November 25, 2013 at New Delhi at p. 17-18 *available at* https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/common_download.jsp?num_id_pk=NzY1.

14. It then took the government till 2015 to publish the draft Drugs & Cosmetics (Second Amendment) Rules, 2015 for comments. These draft rules, if formally enacted, would have required all generic drugs to submit the same stability data as was then required of only 'new drugs' under Appendix IX of Schedule Y. In other words, the manufacturers of all drugs, and not just "new drugs", would have to compulsorily submit data pertaining to "stability testing" to either the CLA or the SLAs. For reasons that were never disclosed, these rules were never formally enacted into law by the government.

15. In June, 2016 I submitted a report to the Ministry of Health where I raised the issue of the lack of mandatory stability testing for all generic drugs in India. I also met with a Joint Secretary in the drug regulation section of the Ministry of Health who assured me that action would be taken on the basis of my report. In that same month, the DTAB at its 72nd meeting[11], discussed the earlier attempts to amend the law to make stability testing a mandatory requirement and noted that the major opposition to the draft amendment published in 2015 was that such a requirement would adversely affect small and medium pharmaceutical units and also increase the cost of majority of medicines. Notwithstanding this opposition, the DTAB once again reiterated its support for amending the law to make it mandatory for all generic drugs to submit stability data as a requirement for approval. Thereafter the DCC took up the same issue at its 50th meeting in November, 2016 and noted that representations had been received from the public about the lack of compulsory stability testing as a perquisite for the grant of a manufacturing licence. Like the DTAB, the DCC once again reiterated its recommendation that stability testing be made mandatory for all generic drugs.

16. On May 2, 2017 the Ministry of Health finally published, for public comment, draft rules proposing to amend the Drugs & Cosmetics Rules, 1945 to make stability testing mandatory. These rules were notified into law on April 10, 2018

[11] Report of the 72nd Meeting of the Drugs Technical Advisory Board (DTAB) held on June 27, 2016 at New Delhi at p. 5 *available at* https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/common_download.jsp?num_id_pk=Nzcy.

as the Drugs & Cosmetics (Third Amendment) Rules, 2018. Surprisingly unlike the draft Drugs & Cosmetics (Second Amendment) Rules, 2015 which had referred to the parameters for stability testing in Appendix IX, the amendments in 2018 were entirely silent on the parameters as per which stability testing is to take place. This created the absurd result of stability testing being compulsory for all generic drugs but without reference to any parameters as per which the testing is to be conducted.

17. Given the absence of any standards or guidance under the Drugs & Cosmetics (Third Amendment) Rules, 2018 on the parameters for stability testing, I submitted a petition to the Health Secretary Preeti Sudan pointing out the minutes of the 53rd meeting of the DCC[12], where it was decided that Smt. Rubina Bose, a Deputy Drugs Controller would produce a "guidance document" to help state authorities implement the mandatory stability requirement. In that petition to Ms. Sudan, I pointed out troubling news reports from Bihar, where pharmaceutical manufacturers were creating trouble after the state drug controller had tried enforcing the mandatory stability testing requirement for all generic drug manufacturers.[13]

18. Since Ms. Sudan did not reply to my petition, I requested colleagues in India to file an application under the Right to Information Act asking for all the file notings related to my petition and also whether any guidance document in relation to stability had in fact been prepared. In response, the Ministry did provide a short guidance document that had been prepared for stability testing of APIs and Finished Pharmaceutical Products (FPP) **(Annexure A1)**. The guidance document which spans a meager four pages, appears to have been hurriedly prepared and is very inadequate when compared to international regulations or the IDMA Guidelines that were proposed in 2002 **(Annexure A2)**.

[12] Report of the 53rd Meeting of the Drugs Consultative Committee (DCC) held on April 9, 2018 at New Delhi at p. 11 *available at* https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/common_download.jsp?num_id_pk=ODE1

[13] Peethaambaran Kunnathoor, 'Drug manufacturers in Bihar to approach DCGI to complain against state DC for anti-industry policies', April 17, 2019 Pharmabiz.com *available at* http://www.pharmabiz.com/NewsDetails.aspx?aid=115253&sid=1

It is quite obvious that the Ministry of Health has not given adequate thought to this vital issue of stability testing. The specific problems with the existing legal framework are detailed in the next section of this petition.

C. <u>The problems with the existing legal framework on stability testing for generic drugs and "new drugs"</u>

19. The existing Indian legal framework regarding stability testing is insufficient for the following reasons:

(a) No testing parameters mentioned for testing the stability of generic drugs that are not "new drugs": As mentioned earlier, one of the obvious shortcomings of the Drugs & Cosmetics (Third Amendment) Rules, 2018 is that it makes no reference to any specific parameters for stability testing. The earlier iteration of this amendment, as found in the draft Drugs & Cosmetics (Second Amendment) Rules, 2015 had referenced parameters laid out for "new drugs" in Appendix IX to Schedule Y to the Drugs & Cosmetics Rules, thereby implying that both "new drugs" and generic drugs would have to follow the same parameters for stability testing. There is no explanation from the government as to why it did away this requirement when it enacted the amendments in 2018. There is no scientific reason for the stability testing parameters to be different for "new drugs" and "generic drugs". The 4 page guidance document (Annexure A1), provided to us is not only inadequate but also lacks the authority of the "law" and is not binding on anybody. Going ahead, the rules will have to be amended to ensure parity between the stability testing regime for "new drugs" and generic drugs.

(b) The stability testing criteria for "new drugs" is inadequate: The stability testing parameters, as laid down for "new drugs" in Clause 5 of the Second Schedule to the New Drugs and Clinical Trial Rules, 2019 while significantly more detailed than the criteria laid down for generic drugs, is inadequate when compared to international standards. To begin with, the stability

guidelines laid down by the World Health Organisation (WHO)[14], treat APIs and Finished Pharmaceutical Products (FPP) as two separate categories that deserve to be treated separately for the purposes of stability testing. For each of these categories, the WHO Guidelines lay down a list of parameters that have to be evaluated. These include, stress testing, selection of batches, container-closure system, specification, testing frequency, storage condition, stability commitments, evaluation, statements and labeling. For FPPs some additional parameters apply such as "in-use and hold time stability" etc. Clause 5, referred to above, vaguely refers to undefined terms such as "drug substances" and "formulations" but without clearly demarcating the requirements for each category as done by the WHO rules. The mass of text in Clause 5 is reflective of the poor drafting quality of Indian regulations and it does not provide clarity or predictably, required for efficient regulation. The government must consider publishing a new set of regulations that provide more clarity and predictably on the issue of stability testing for both APIs and FPP (both new drugs and generics).

(c) No mention of documentation requirements for stability testing: One of the fundamental building blocks of a successful regulatory framework is documentation or a paper trail that has been mandated by the law. This is especially true for the pharmaceutical industry. Under American law for instance, pharmaceutical companies are required to prepare a "written testing program" for establishing the stability of each drug product.[15] This program includes the statistical criteria for sampling from each batch, storage conditions for retained samples, reliable test methods, testing of drug products in the packaging that there are being sold in and testing of drug products after reconstitution. Creating such written records within pharmaceutical companies is important because it enables regulators to

[14] 52nd Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations *available at* https://extranet.who.int/prequal/sites/default/files/documents/TRS1010_Annex10.pdf
[15] 21 CFR 4 – Sec. 211.166 *available at* https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.166.

conduct inspections and trace the source of problem in case a batch tests as 'not-of-standard' quality. The Drugs and Cosmetics Rules, 1945 and the New Drugs and Clinical Trial Rules, 2019 are silent on the documentation requirement for stability studies that are conducted on APIs and FPPs. This needs to be rectified urgently by amending the law to mandate the creation of records to track stability testing. The New Drugs and Clinical Trial Rules, 2019 need to specify how the conditions within the stability chambers are monitored and recorded and the timelines according to which the samples from the stability chambers are to be analyzed for degradation impurities. Such detail cannot be left to the interpretation of individual manufacturers.

(d) Lack of penalties for entities that fabricate stability data or fail to conduct stability testing: As mentioned earlier, one of the recurring issues during USFDA inspections of Indian pharmaceutical manufacturing plants was data fabrication in relation to stability tests. These companies were presumably fabricating data either because they lacked the time given their shipping schedules or more likely because the batches of product in question failed stability testing and rather than destroy the batches as per protocol, the data was fabricated to justify release of those batches into the market. As per American law, the sale of drugs, which have not been manufactured as per the prescribed good manufacturing practices are presumed to be adulterated. It was therefore possible for the United States to charge Ranbaxy for selling adulterated drugs because it either skipped or fabricated stability testing for several batches.[16] Unfortunately, India does not have similar laws or penalties for pharmaceutical companies that either skip or fabricate, data related to stability testing. It would thus be prudent to amend Indian law on this point to introduce stringent penalties for companies that either fabricate or omit stability studies.

[16] Plea Agreement between the Department of Justice, United States and Ranbaxy USA Inc. in the case of United States v. Ranbaxy Inc. dated January 2, 2013 *available at* https://dineshthakur.com/wp-content/uploads/2013/05/2013.05.13-Ranbaxy-Plea-Agreement.pdf.

(e) Silence on strategies to tackles rampant data fabrication: While the above discussed strategy to penalize data fabrication is one way to tackle data fabrication, Indian law also has to adopt other measures that makes data fabrication more difficult to commit and perhaps, easier for regulators to detect. This is because getting evidence of data fabrication is not always easy. One way to make it tougher for companies to fabricate data is to require the mandatory adoption of software programs that maintain a tamperproof audit trail. An example of this is a continuous chart-recorder of the temperature & humidity of the stability chambers. Allowing manual recording of discrete observations of such measurement by scientists makes it possible to fabricate data. Use of automated probes that record such observations on a continual basis which can be audited is a much more effective way of ensuring compliance with regulations. This is of course no guarantee against all forms of data fabrications but is merely one possible idea to tackle the problem. It is necessary for Indian regulators to discuss this issue in more detail and codify any possible solutions into the language of the law.

(f) Silence on drug batches already approved: Although the government has theoretically made stability testing compulsory for all new generic drugs, there is no mention of drugs that have already received marketing approval. Given the importance of stability testing in ensuring quality control, it should be necessary for regulators to apply this quality measure retrospectively, requiring all manufacturers to submit stability data for their drugs, which received approval prior to the amendments of 2018 to the Drugs & Cosmetics Rules, 1945.

(g) Silence on a mandate to test every batch for stability: The amendments in 2018, which made it mandatory for stability testing as a precondition to receiving a manufacturing licence from State Licensing Authorities (SLAs) are silent on the requirement to conduct such stability testing on each batch post

the grant of a manufacturing silence. This is a puzzling silence since most countries require pharmaceutical manufacturers to test the stability of each batch and store the information for future inspections. The lack of a similar requirement in Indian law is a serious lacunae because each batch of drugs can differ from the other.

(h) Lack of testing protocols for stability in Indian laboratories: One of the principal modes of enforcement of Indian drug regulatory laws when it comes to drug quality is by testing samples drawn from the market by government laboratories. The only way to really test the stability of drugs is by checking each sample for presence of impurities from degradation of the drug product i.e., if the drug has not been formulated as per specifications, impurities resulting from degradation of API, excipients will show up during the testing process. The problem however is all Indian government laboratories test only for assay and dissolution and not the impurity profiles of the drugs. Even in cases where the government analyst is able to visually observe discoloration of a tablet for example, they do not conduct an investigation into the root-cause to examine the nature of the impurity and its source as to whether it is linked to the stability of the product. This must change because ensuring stability is one of the biggest manufacturing challenges faced by the pharmaceutical industry.

(i) Failure to revise Labeling requirements in Schedule P: Stability testing should ideally be linked to labeling requirements. Under Indian law, Schedule P to the Drugs & Cosmetics Rules, 1945, read in conjunction with Rule 96 mandates all manufacturers to print on the packaging, information related to the expiry date and conditions of storage mentioned in Schedule P. For example, for Ampicillin, Schedule P states that the expiry date should be 36 months from the date of manufacture and the conditions of storage should be "In a cool place". Such vague instructions are not helpful because many temperature sensitive drugs will disintegrate if not stored in specific

controlled temperatures. In a complicated market like India where supply chains extend into small towns and villages, it is even more important to ensure that pharmaceutical companies are mandated to publish more accurate storage information on their labeling in order to ensure that pharmacists and patients are equipped with better information to prevent unintended degradation of drugs. This information should ideally be linked to the standards prescribed in the Indian Pharmacopeia.

D. Recommendation for Ensuring Greater Clarity and Consistency of India's Stability Testing Norms

20. Given the various lacunae and issues with the Indian law on the stability testing, we request you to setup an inter-disciplinary Committee of Experts consisting of pharmacists, pharmacologists, doctors and lawyers to specifically study the following issues and submit a report to the Ministry:

(a) Do the New Drugs and Clinical Trial Rules, 2019 provide clear and cogent guidance on stability testing when compared to the WHO and USFDA regulations on the same point?

(b) How can the Drugs & Cosmetics (Third Amendment) Rules, 2018 be amended to provide sufficient clarity on the parameters for stability testing of generic medicines?

(c) What should be the mandatory documentation that companies should be required to generate and store with regard to their internal stability testing?

(d) Should the criteria for stability testing be different for "new drugs" and "generic drugs"?

(e) Should Indian law be amended to mandatorily require stability testing of every batch of drugs by the Indian pharmaceutical industry?

(f) Should Indian law be amended to mandatorily require government laboratories to test samples drawn from the market, for impurities?

(g) Should Indian law on packaging of drugs be amended to require the publication of more accurate storage conditions?

(h) Should the failure to conduct stability testing for a batch of drugs before they are released in the market be equated to the sale of adulterated drugs?

(i) How best can the law deter the fabrication or manipulation of data related to stability testing?

I 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